ABSORICA- is otretinoin capsule Ranbaxy Laboratories Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ABSORICA safely and effectively. See full prescribing information for ABSORICA.

ABSORICA® (isotretinoin) capsules, for oral use

Initial U.S. Approval: 1982

WARNING: CAUSES BIRTH DEFECTS

See full prescribing information for complete boxed warning.

Pregnancy Category X.

- ABSORICA must not be used by female patients who are or may become pregnant (5, 8.1, 8.6).
- There is an extremely high risk that severe birth defects will result if pregnancy occurs while taking ABSORICA in any amount, even for short periods of time. Potentially any fetus exposed during pregnancy can be affected (5.1, 8.1).
- There are no accurate means of determining whether an exposed fetus has been affected (5.1, 8.1).
- ABSORICA is available only through a restricted program called the iPLEDGE program. Prescribers, patients, pharmacies, and distributors must enroll in the program (5.2).

------ INDICATIONS AND USAGE ·-----

ABSORICA is a retinoid indicated for the treatment of severe recalcitrant nodular acne in patients 12 years of age and older (1).

Limitations of Use

ABSORICA may only be administered to patients enrolled in the iPLEDGE program (1, 5.2).

-----DOSAGE AND ADMINIST RATION ------

- Recommended dosage of 0.5 to 1 mg/kg/day given in two divided doses without regards to meals for 15 to 20 weeks (2.1).
- Once daily dosing is **not** recommended (2.1).
- Perform pregnancy tests prior to prescribing, each month during therapy, end of therapy, and one month after discontinuation (2.4, 8.6).
- Prior to prescribing, perform fasting lipid profile and liver function tests (2.4).
- ABSORICA is not substitutable with other forms of isotretinoin (12.3).

----- DOSAGE FORMS AND STRENGTHS -----

Capsules: 10 mg, 20 mg, 25 mg, 30 mg, 35 mg and 40 mg (3)

------CONTRAINDICATIONS ------

- Pregnancy (4.1, 8.1)
- Hypersensitivity to this product or any of its components (4.2, 5.14)

------ WARNINGS AND PRECAUTIONS -----

- Unacceptable Contraception: Micro-dosed progesterone preparations are not an acceptable method of contraception during ABSORICA therapy (5.3)
- Psychiatric Disorders: Depression, psychosis, suicidal thoughts and behavior, and aggressive and/or violent behaviors (5.4)
- Pseudotumor cerebri, some cases with concomitant tetracyclines (5.5)
- Serious skin reactions: Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) (5.6)
- Acute pancreatitis, rarely fatal hemorrhagic pancreatitis, in patients with either elevated or normal serum triglyceride levels (5.7)
- Lipid Abnormalities: Triglyceridemia low HDL and elevation of cholesterol. Monitor lipid levels at regular intervals (5.8, 5.15)
- Hearing Impairment (5.9)

- Hepatotoxicity: Monitor liver function tests at regular intervals (5.10, 5.15)
- Inflammatory Bowel Disease (5.11)
- Skeletal Abnormalities: Arthralgias, back pain, decreases in bone mineral density and premature epiphyseal closure (5.12)
- Ocular Abnormalities: corneal opacities, decreased night vision (5.13)
- Glucose and CPK Abnormalities (5.15)

------ ADVERSE REACTIONS ------

Most common adverse reactions (incidence ≥5%) are: lip dry, dry skin, back pain, dry eye, arthralgia, epistaxis, headache, nasopharyngitis, chapped lips, dermatitis, blood creatine kinase increased, cheilitis, musculoskeletal discomfort, upper respiratory tract infection, visual acuity reduced (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Ranbaxy, Inc. at 1-800-406-7984 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch or iPLEDGE at (1-866-495-0654).

------ DRUG INTERACTIONS ------

- Vitamin A: may cause additive adverse reactions (7.1)
- Tetracyclines: avoid concomitant use (7.2)
- St. John's Wort: may interfere with oral contraceptives (7.4)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 8/2014

FULL PRESCRIBING INFORMATION: CONTENTS* WARNING: CAUSES BIRTH DEFECTS

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

- 2.1 Recommended Dosage
- 2.2 Dosage Range
- 2.3 Duration of Use
- 2.4 Laboratory Testing

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

- 4.1 Pregnancy
- 4.2 Hypersensitivity

5 WARNINGS AND PRECAUTIONS

- 5.1 Embryofetal Toxicity
- 5.2 iPLEDGE Program
- 5.3 Unacceptable Contraception
- 5.4 Psychiatric Disorders
- 5.5 Pseudotumor Cerebri
- 5.6 Serious Skin Reactions
- 5.7 Pancreatitis
- 5.8 Lipid Abnormalities
- 5.9 Hearing Impairment
- 5.10 Hepatotoxicity
- 5.11 Inflammatory Bowel Disease
- 5.12 Skeletal Abnormalities
- 5.13 Ocular Abnormalities
- 5.14 Hypersensitivity
- 5.15 Laboratory Monitoring for Adverse Reactions

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

7 DRUG INTERACTIONS

- 7.1 Vitamin A
- 7.2 Tetracyclines
- 7.3 Phenytoin
- 7.4 St. John's Wort
- 7.5 Systemic Corticosteroids
- 7.6 Norethindrone/ethinyl estradiol

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Females of Childbearing Potential

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis and Impairment of Fertility
- 13.2 Animal Toxicology

14 CLINICAL STUDIES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

FULL PRESCRIBING INFORMATION

^{*} Sections or subsections omitted from the full prescribing information are not listed.

WARNING: CAUSES BIRTH DEFECTS

Pregnancy Category X.

- ABSORICA must not be used by female patients who are or may become pregnant [seeWarnings and Precautions (5) and Use in Specific Populations (8.1, 8.6)].
- There is an extremely high risk that severe birth defects will result if pregnancy occurs while taking ABSORICA in any amount, even for short periods of time [seeWarnings and Precautions (5.1) and Use in Specific Populations (8.1)].
- Potentially any fetus exposed during pregnancy can be affected [seeUse in Specific Populations(8.1)].
- There are no accurate means of determining whether an exposed fetus has been affected [seeWarning and Precautions (5.1) and Use in Specific Populations (8.1)].
- Birth defects which have been documented following is otretinoin exposure include abnormalities of the face, eyes, ears, skull, central nervous system, cardiovascular system, and thymus and parathyroid glands. Cases of IQ scores less than 85 with or without other abnormalities have been reported. There is an increased risk of spontaneous abortion and premature births have been reported [seeUse in Specific Populations(8.1)].
- Documented external abnormalities include: skull abnormality; ear abnormalities (including anotia, micropinna, small or absent external auditory canals); eye abnormalities (including microphthalmia; facial dysmorphia; cleft palate). Documented internal abnormalities include: CNS abnormalities (including cerebral abnormalities, cerebellar malformation, hydrocephalus, microcephaly, cranial nerve deficit); cardiovas cular abnormalities; thymus gland abnormality; parathyroid hormone deficiency. In some cases death has occurred with certain abnormalities previously noted [seeUse in Specific Populations (8.1)].
- If pregnancy does occur during the treatment of a female patient who is taking ABSORICA, ABSORICA must be discontinued immediately and she should be referred to an Obstetrician-Gynecologist experienced in reproductive toxicity for further evaluation and counseling [seeUse in Specific Populations (8.1)].

Special Prescribing Requirements

• Because of the risk of teratogenicity and to minimize fetal exposure, ABSORICA is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called iPLEDGE™. Under the ABSORICA REMS, prescribers, patients, pharmacies, and distributors must enroll and be registered in the program [seeWarnings and Precautions (5.2)].

1 INDICATIONS AND USAGE

ABSORICA is a retinoid indicated for the treatment of severe recalcitrant nodular acne in patients 12 years of age and older. Nodules are inflammatory lesions with a diameter of 5 mm or greater. The nodules may become suppurative or hemorrhagic. "Severe," by definition, means "many" as opposed to "few or several" nodules. Because of significant adverse reactions associated with its use, ABSORICA should be reserved for patients with multiple severe nodular acne who are unresponsive to conventional therapy, including systemic antibiotics. In addition, ABSORICA is indicated only for those female patients who are not pregnant, because ABSORICA can cause severe birth defects [see *Contraindications* (4.1)].

Limitations of Use

A single course of therapy for 15 to 20 weeks has been shown to result in complete and prolonged remission of disease in many patients. If a second course of therapy is needed, it should not be initiated until at least 8 weeks after completion of the first course, because experience with isotretinoin has shown that patients may continue to improve following treatment with isotretinoin. The optimal interval before retreatment has not been defined for patients who have not completed skeletal growth [seeWarnings and Precautions (5.12)].

As a part of the iPLEDGE program, ABSORICA may only be administered to patients enrolled in the program [seeWarnings and Precautions (5.2)].

2 DOSAGE AND ADMINISTRATION

Healthcare professionals who prescribe ABSORICA must be certified in the iPLEDGE program and must comply with the required monitoring to ensure safe use of ABSORICA [see *Warnings and Precautions* (5.2)].

The required laboratory testing must be completed prior to dosing ABSORICA [see *Dosage and Administration* (2.4)].

Pregnancy Testing, and Contraceptive measures must be followed prior to dosing ABSORICA [seeUse in Specific Populations (8.6)].

2.1 Recommended Dosage

The recommended dosage range for ABSORICA is 0.5 to 1 mg/kg/day given in two divided doses without regard to meals for 15 to 20 weeks (see Table 1). To decrease the risk of esophageal irritation, patients should swallow the capsules with a full glass of liquid [seePatient Counseling Information (17)].

The safety of once daily dosing with ABSORICA has not been established. Once daily dosing is **not** recommended.

Body Weight		,		
Kilograms	Pounds	0.5 mg/kg	1 mg/kg	2 mg/kg
40	88	20	40	80
50	110	25	50	100
60	132	30	60	120
70	154	35	70	140
80	176	40	80	160
90	198	45	90	180
100	220	50	100	200

Table 1: ABSORICA Dosing by Body Weight (Based on Administration With or Without Food)

2.2 Dosage Range

In trials comparing 0.1, 0.5, and 1 mg/kg/day, it was found that all dosages provided initial clearing of disease, but there was a greater need for retreatment with the lower dosages. During treatment, the dose may be adjusted according to response of the disease and/or the appearance of clinical side effects, some of which may be dose-related. Adult patients whose disease is very severe with scarring or is primarily manifested on the trunk may require dose adjustments up to 2 mg/kg/day, as tolerated.

2.3 Duration of Use

A normal course of treatment is 15 - 20 weeks. If the total nodule count has been reduced by more than 70% prior to completing 15 to 20 weeks of treatment, the drug may be discontinued. After a period of 2

months or more off therapy, and if warranted by persistent or recurring severe nodular acne, a second course of therapy may be initiated. The optimal interval before retreatment has not been defined for patients who have not completed skeletal growth. Long-term use of ABSORICA, even in low doses, has not been studied, and is not recommended. It is important that ABSORICA be given at the recommended doses for no longer than the recommended duration. The effect of long-term use of ABSORICA on bone loss is unknown [seeWarnings and Precautions (5.12)].

2.4 Laboratory Testing

Pregnancy Testing

[SeeUse in Specific Populations (8.6)]

Lipid Profile

Perform a fasting lipid profile including triglycerides prior to use of ABSORICA [seeWarnings and *Precautions* (5.8, 5.15)].

Liver Function Test

Perform liver function tests prior to use of ABSORICA [seeWarnings and Precautions (5.10, 5.15)].

3 DOSAGE FORMS AND STRENGTHS

ABSORICA is available in 10 mg, 20 mg, 25 mg, 30 mg, 35 mg and 40 mg capsules.

- **10 mg:** Dark yellow, opaque, capsule imprinted with black ink "**G 240**" on cap and "**10**" on the body
- **20 mg:** Red, opaque, capsule imprinted with black ink "**G 241**" on cap and "**20**" on the body
- 25 mg: Green, opaque, capsule imprinted with white ink "G 342" on cap and "25" on the body
- **30 mg:** Brown, opaque, capsule imprinted with white ink "**G 242**" on cap and "**30**" on the body
- 35 mg: Dark blue, opaque, capsule imprinted with white ink "G 343" on cap and "35" on the body
- **40 mg:** Brown and red, capsule imprinted with white ink "G 325" on cap and "40" on the body

4 CONTRAINDICATIONS

4.1 Pregnancy

ABSORICA can cause fetal harm when administered to a pregnant woman. Major congenital malformations, spontaneous abortions, and premature births have been documented following pregnancy exposure to isotretinoin in any amount and even for short periods of time. ABSORICA is contraindicated in females who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, treatment should be discontinued and the patient should be apprised of the potential hazard to the fetus [seeUse in Specific Populations (8.1)].

4.2 Hypersensitivity

Hypersensitivity to this product (or Vitamin A, given the chemical similarity to isotretinoin) or to any of its components [seeWarnings and Precautions (5.14)].

5 WARNINGS AND PRECAUTIONS

ABSORICA must not be used by female patients who are or may become pregnant. There is an extremely high risk that severe birth defects will result if pregnancy occurs while taking ABSORICA in any amount, even for short periods of time.

5.1 Embryofetal Toxicity

Teratogenicity

Major congenital malformations, spontaneous abortions, and premature births have been documented following pregnancy exposure to isotretinoin [seeUse in Specific Populations (8.1)]. Females of childbearing potential must comply with the pregnancy testing and contraception requirements described in the iPLEDGE program [seeWarnings and Precautions (5.2) and Use in Specific Populations (8.6)]. There are no accurate means of determining whether an exposed fetus has been affected.

No Blood Donation

Patients must be informed not to donate blood during isotretinoin therapy and for 1 month following discontinuation of the drug because the blood might be given to a pregnant female patient whose fetus must not be exposed to isotretinoin.

5.2 iPLEDGE Program

Because of the risk of teratogenicity and to minimize fetal exposure, ABSORICA is available only through a restricted program under a REMS called iPLEDGE. Under the ABSORICA REMS, prescribers, patients, pharmacies, and distributors must enroll and be registered in the program. ABSORICA must not be prescribed, dispensed or otherwise obtained through the internet or any other means outside of the iPLEDGE program. Only FDA-approved isotretinoin products must be distributed, prescribed, dispensed, and used.

Required components of the iPLEDGE Program are:

- ABSORICA must only be prescribed by prescribers who are registered and activated with the
 iPLEDGE program and agree to comply with the REMS requirements described in the booklets
 entitled The Guide to Best Practices for the iPLEDGE Program, The iPLEDGE Program Prescriber
 Contraception Counseling Guide, and Recognizing Psychiatric Disorders in Adolescents and Young
 Adults: A Guide for Prescribers of Isotretinoin.
- Male patients and Female patients <u>not</u> of childbearing potential: To obtain ABSORICA, these patients must understand the risks and benefits of ABSORICA, comply with the REMS requirements described in the booklet entitled *The iPLEDGE Program Guide to Isotretinoin for Male Patients and Female Patients Who Cannot Get Pregnant*, and sign a Patient Information/Informed Consent form.
- Female patients of childbearing potential: ABSORICA is contraindicated in female patients who are or may become pregnant [seeContraindications (4.1)].
- Female patients of childbearing potential who are <u>not</u> pregnant must understand the risks and benefits, comply with the REMS requirements described in the booklet entitled *The iPLEDGE Program Guide to Isotretinoin for Female Patients Who Can Get Pregnant* and *The iPLEDGE Program Birth Control Workbook* (including the pregnancy testing and contraception requirements [seeUse in Specific Populations (8.6) and Patient Counseling Information (17)]), and sign a Patient Information/Informed Consent form and Patient Information/Informed Consent About Birth Defects form. Additionally, the patient must answer questions about the iPLEDGE program and pregnancy prevention monthly.
- Pharmacies that dispense ABSORICA must be registered and activated with iPLEDGE, must only
 dispense to patients who are authorized to receive ABSORICA, and agree to comply with the
 REMS requirements described in the booklet entitled *The Pharmacist Guide for the iPLEDGE*Program.
- Female patients of childbearing potential must fill and pick up the prescription within 7 days of the specimen collection for the pregnancy test; male patients and female patients not of childbearing potential must fill and pick up the prescription within 30 days of the office visit.
- ABSORICA must only be dispensed in no more than a 30-day supply with a Medication Guide.

- Refills require a new prescription and a new authorization from the iPLEDGE system.
- Wholesalers and distributors that distribute ABSORICA must be registered with iPLEDGE and agree to comply with the REMS requirements.

If a pregnancy does occur during ABSORICA treatment, ABSORICA must be discontinued immediately. The patient should be referred to an obstetrician-gynecologist experienced in reproductive toxicity for further evaluation and counseling. Any suspected fetal exposure during or 1 month after ABSORICA therapy must be reported immediately to the FDA via the MedWatch telephone number 1-800-FDA-1088 and also to the iPLEDGE pregnancy registry at 1-866-495-0654 or via the internet (www.ipledgeprogram.com).

Further information, including a list of qualified pharmacies, is available at www.ipledgeprogram.com or 1-866-495-0654.

5.3 Unacceptable Contraception

Micro-dosed Progesterone Preparations

Micro-dosed progesterone preparations ("minipills" that do not contain an estrogen) are an inadequate method of contraception during ABSORICA therapy.

5.4 Psychiatric Disorders

Isotretinoin may cause depression, psychosis and, rarely, suicidal ideation, suicide attempts, suicide, and aggressive and/or violent behaviors. No mechanism of action has been established for these reactions [seeAdverse Reactions (6.1)]. Prescribers should read the brochure, Recognizing Psychiatric Disorders in Adolescents and Young Adults: A Guide for Prescribers of Isotretinoin. Prescribers should be alert to the warning signs of psychiatric disorders to guide patients to receive the help they need. Therefore, prior to initiation of ABSORICA therapy, patients and family members should be asked about any history of psychiatric disorder, and at each visit during therapy patients should be assessed for symptoms of depression, mood disturbance, psychosis, or aggression to determine if further evaluation may be necessary. Signs and symptoms of depression, as described in the brochure (Recognizing Psychiatric Disorders in Adolescents and Young Adults), include sad mood, hopelessness, feelings of guilt, worthlessness or helplessness, loss of pleasure or interest in activities, fatigue, difficulty concentrating, change in sleep pattern, change in weight or appetite, suicidal thoughts or attempts, restlessness, irritability, acting on dangerous impulses, and persistent physical symptoms unresponsive to treatment. Patients should stop ABSORICA and the patient or a family member should promptly contact their prescriber if the patient develops depression, mood disturbance, psychosis, or aggression, without waiting until the next visit. Discontinuation of ABSORICA therapy may be insufficient; further evaluation may be necessary. While such monitoring may be helpful, it may not detect all patients at risk. Patients may report mental health problems or family history of psychiatric disorders. These reports should be discussed with the patient and/or the patient's family. A referral to a mental health professional may be necessary. The physician should consider whether ABSORICA therapy is appropriate in this setting; for some patients the risks may outweigh the benefits of ABSORICA therapy.

5.5 Pseudotumor Cerebri

Isotretinoin use has been associated with cases of pseudotumor cerebri (benign intracranial hypertension), some of which involved concomitant use of tetracyclines. Concomitant treatment with tetracyclines should therefore be avoided. Early signs and symptoms of pseudotumor cerebri include papilledema, headache, nausea and vomiting, and visual disturbances. Patients with these symptoms should be screened for papilledema and, if present, they should be told to discontinue ABSORICA immediately and be referred to a neurologist for further diagnosis and care [seeAdverse Reactions (6.1)].

5.6 Serious Skin Reactions

There have been post-marketing reports of erythema multiforme and severe skin reactions [e.g., Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN)] associated with isotretinoin use. These reactions may be serious and result in death, life-threatening events, hospitalization, or disability. Patients should be monitored closely for severe skin reactions, and discontinuation of ABSORICA should be considered if warranted.

5.7 Pancreatitis

Acute pancreatitis has been reported in isotretinoin-treated patients with either elevated or normal serum triglyceride levels. In rare instances, fatal hemorrhagic pancreatitis has been reported. ABSORICA should be stopped if hypertriglyceridemia cannot be controlled at an acceptable level or if symptoms of pancreatitis occur.

5.8 Lipid Abnormalities

Elevations of serum triglycerides in excess of 800 mg/dL have been reported in patients treated with isotretinoin. Marked elevations of serum triglycerides were reported in approximately 25% of patients receiving isotretinoin in clinical trials. In addition, approximately 15% developed a decrease in high-density lipoproteins and about 7% showed an increase in cholesterol levels. In clinical trials, the effects of triglycerides, HDL and cholesterol were reversible upon cessation of isotretinoin therapy. Some patients have been able to reverse triglyceride elevation by reduction in weight, restriction of dietary fat and alcohol, and reduction in the dose while continuing isotretinoin.

Blood lipid determinations should be performed before ABSORICA is given and then at intervals until the lipid response to ABSORICA is established, which usually occurs within 4 weeks. Especially careful consideration must be given to risk/benefit for patients who may be at high risk of triglyceridemia during ABSORICA therapy (patients with diabetes, obesity, increased alcohol intake, lipid metabolism disorder or familial history of lipid metabolism disorder). If ABSORICA therapy is instituted, more frequent checks of serum values for lipids and/or blood sugar are recommended [seeWarnings and Precautions (5.15)].

The cardiovascular consequences of hypertriglyceridemia associated with isotretinoin are unknown.

5.9 Hearing Impairment

Impaired hearing has been reported in patients taking isotretinoin; in some cases, the hearing impairment has been reported to persist after therapy has been discontinued. Mechanism(s) and causality for this reaction have not been established. Patients who experience tinnitus or hearing impairment should discontinue ABSORICA treatment and be referred for specialized care for further evaluation [seeAdverse Reactions (6.1)].

5.10 Hepatotoxicity

Clinical hepatitis considered to be possibly or probably related to isotretinoin therapy has been reported. Additionally, mild to moderate elevations of liver enzymes have been observed in approximately 15% of individuals treated during clinical trials with isotretinoin, some of which normalized with dosage reduction or continued administration of the drug. If normalization does not readily occur or if hepatitis is suspected during treatment with ABSORICA, the drug should be discontinued and the etiology further investigated.

5.11 Inflammatory Bowel Disease

Isotretinoin has been associated with inflammatory bowel disease (including regional ileitis) in patients without a prior history of intestinal disorders. In some instances, symptoms have been reported to persist after isotretinoin treatment has been stopped. Patients experiencing abdominal pain, rectal bleeding or severe diarrhea should discontinue ABSORICA immediately [seeAdverse Reactions (6.1)].

5.12 Skeletal Abnormalities

Bone Mineral Density Changes

Isotretinoin may have a negative effect on bone mineral density (BMD) in some patients. In a clinical trial of ABSORICA and a generic product of Accutane (isotretinoin), 27/306 (8.8%) of adolescents had BMD declines, defined as $\geq 4\%$ lumbar spine or total hip, or $\geq 5\%$ femoral neck, during the 20 week treatment period. Repeat scans conducted within 2-3 months after the post-treatment scan showed no recovery of BMD. Longer term data at 4-11 months showed that 3 out of 7 patients had total hip and femoral neck BMD below pre-treatment baseline, and 2 others did not show the increase in BMD above baseline expected in this adolescent population. Therefore, physicians should use caution when prescribing ABSORICA to patients with a history of childhood osteoporosis conditions, osteomalacia, or other disorders of bone metabolism. This would include patients diagnosed with anorexia nervosa and those who are on chronic drug therapy that causes drug-induced osteoporosis/osteomalacia and/or affects vitamin D metabolism, such as systemic corticosteroids and any anticonvulsant [see Use in Specific Populations (8.4)].

Musculos keletal Abnormalities

Approximately 16% of patients treated with isotretinoin in a clinical trial developed musculoskeletal symptoms (including arthralgia) during treatment. In general, these symptoms were mild to moderate, but occasionally required discontinuation of the drug.

In a trial of pediatric patients treated with isotretinoin, approximately 29% (104/358) developed back pain. Back pain was severe in 13.5% (14/104) of the cases and occurred at a higher frequency in female patients than male patients. Arthralgias were experienced in 22% (79/358) of pediatric patients. Arthralgias were severe in 7.6% (6/79) of patients. Appropriate evaluation of the musculoskeletal system should be done in patients who present with these symptoms during or after a course of ABSORICA. Consideration should be given to discontinuation of ABSORICA if any significant abnormality is found.

There have been spontaneous reports of osteoporosis, osteopenia, bone fractures and/or delayed healing of bone fractures in patients while on therapy with isotretinoin or following cessation of therapy with isotretinoin. While causality to isotretinoin has not been established, an effect cannot be ruled out.

Patients may be at an increased risk when participating in sports with repetitive impact where the risks of spondylolisthesis with and without pars fractures and hip growth plate injures in early and late adolescence are known.

Effects of multiple courses of isotretinoin on the developing musculoskeletal system are unknown. There is some evidence that long-term, high-dose, or multiple courses of therapy with isotretinoin have more of an effect than a single course of therapy on the musculoskeletal system.

Longer term effects have not been studied. It is important that ABSORICA be given at the recommended doses for no longer than the recommended duration.

Hyperostosis

A high prevalence of skeletal hyperostosis was noted in clinical trials for disorders of keratinization with a mean dose of 2.24 mg/kg/day of isotretinoin. Additionally, skeletal hyperostosis was noted in 6 of 8 patients in a prospective trial of disorders of keratinization. Minimal skeletal hyperostosis and calcification of ligaments and tendons have also been observed by x-ray in prospective trials of nodular acne patients treated with a single course of therapy at recommended doses. The skeletal effects of multiple isotretinoin treatment courses for acne are unknown.

In a clinical trial of 217 pediatric patients (12 to 17 years) with severe recalcitrant nodular acne, hyperostosis was not observed after 16 to 20 weeks of treatment with approximately 1 mg/kg/day of isotretinoin given in two divided doses. Hyperostosis may require a longer time frame to appear. The clinical course and significance remain unknown.

Premature Epiphyseal Closure

There are spontaneous literature reports of premature epiphyseal closure in acne patients receiving recommended doses of isotretinoin. The effect of multiple courses of isotretinoin on epiphyseal closure is unknown.

In a 20-week clinical trial that included 289 adolescents on ABSORICA or a generic product of Accutane[®] (isotretinoin) who had hand radiographs taken to assess bone age, a total of 9 (3.11%) patients had bone age changes that were clinically significant and for which a drug-related effect cannot be excluded.

5.13 Ocular Abnormalities

Visual problems should be carefully monitored. All ABSORICA patients experiencing visual difficulties should discontinue ABSORICA treatment and have an ophthalmological examination [see Adverse Reactions (6.1)].

Corneal Opacities

Corneal opacities have occurred in patients receiving isotretinoin for acne and more frequently when higher drug dosages were used in patients with disorders of keratinization. The corneal opacities that have been observed in clinical trial patients treated with isotretinoin have either completely resolved or were resolving at follow-up 6 to 7 weeks after discontinuation of the drug [see Adverse Reactions (6.1)].

Decreased Night Vision

Decreased night vision has been reported during isotretinoin therapy and in some instances the event has persisted after therapy was discontinued. Because the onset in some patients was sudden, patients should be advised of this potential problem and warned to be cautious when driving or operating any vehicle at night.

Dry Eye

Dry eye has been reported in subjects during isotretinoin therapy. Patients who wear contact lenses may have trouble wearing them while on ABSORICA treatment and afterwards.

5.14 Hypersensitivity

Anaphylactic reactions and other allergic reactions have been reported in isotretinoin-treated patients. Cutaneous allergic reactions and serious cases of allergic vasculitis, often with purpura (bruises and red patches) of the extremities and extracutaneous involvement (including renal) have been reported. Severe allergic reaction necessitates discontinuation of therapy and appropriate medical management.

5.15 Laboratory Monitoring for Adverse Reactions

Lipids Test

Pretreatment and follow-up blood lipids should be obtained under fasting conditions. After consumption of alcohol, at least 36 hours should elapse before these determinations are made. It is recommended that these tests be performed at weekly or biweekly intervals until the lipid response to ABSORICA is established. The incidence of hypertriglyceridemia is 1 patient in 4 on isotretinoin [see Warnings and Precautions (5.8)].

Liver Function Test

Since elevations of liver enzymes have been observed during clinical trials, and hepatitis has been reported in patients on isotretinoin, pretreatment and follow-up liver function tests should be performed at weekly or biweekly intervals until the response to ABSORICA has been established [see Warnings and Precautions (5.10)].

Glucose

Some patients receiving isotretinoin have experienced problems in the control of their blood sugar. In addition, new cases of diabetes have been diagnosed during isotretinoin therapy, although no causal relationship has been established.

CPK

Some patients undergoing vigorous physical activity while on isotretinoin therapy have experienced elevated CPK levels; however, the clinical significance is unknown. There have been rare postmarketing reports of rhabdomyolysis, some associated with strenuous physical activity. In an isotretinoin clinical trial of 924 patients, marked elevations in CPK (≥350 U/L) were observed in approximately 24% of patients. In another clinical trial of 217 pediatric patients (12 − 17 years) elevations in CPK were observed in 12% of patients, including those undergoing strenuous physical activity in association with reported musculoskeletal adverse events such as back pain, arthralgia, limb injury, or muscle sprain. In these patients, approximately half of the CPK elevations returned to normal within 2 weeks and half returned to normal within 4 weeks. No cases of rhabdomyolysis were reported in this clinical trial.

6 ADVERSE REACTIONS

The following adverse reactions with ABSORICA or other isotretinoin products are described in more detail in other sections of the labeling:

- Embryofetal Toxicity [see Warnings and Precautions (5.1)]
- Psychiatric Disorders [see Warnings and Precautions (5.4)]
- Pseudotumor Cerebri [see Warnings and Precautions (5.5)]
- Serious Skin Reactions [see *Warnings and Precautions* (5.6)]
- Pancreatitis [see Warnings and Precautions (5.7)]
- Lipid Abnormalities [see Warnings and Precautions (5.8)]
- Hearing Impairment [see Warnings and Precautions (5.9)]
- Hepatotoxicity [see Warnings and Precautions (5.10)]
- Inflammatory Bowel Disease [see Warnings and Precautions (5.11)]
- Skeletal Abnormalities [see Warnings and Precautions (5.12)]
- Ocular Abnormalities [see Warnings and Precautions (5.13)]
- Hypersensitivity [see Warnings and Precautions (5.14)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of ABSORICA cannot be directly compared to rates in clinical trials of other drugs and may not reflect the rates observed in practice.

The adverse reactions listed below reflect both clinical experience with ABSORICA, and consider other adverse reactions that are known from clinical trials and the post-marketing surveillance with oral isotretinoin. The relationship of some of these events to isotretinoin therapy is unknown. Many of the side effects and adverse events seen in patients receiving isotretinoin are similar to those described in patients taking very high doses of vitamin A (dryness of the skin and mucous membranes, e.g., of the lips, nasal passage, and eyes).

Dose Relationship

Cheilitis and hypertriglyceridemia are adverse reactions that are usually dose related. Most adverse reactions reported in clinical trials with isotretinoin were reversible when therapy was discontinued; however, some persisted after cessation of therapy.

Body as a Whole

The following adverse reactions have been reported in a clinical trial conducted with ABSORICA and a generic product of Accutane[®] (isotretinoin): fatigue, irritability, pain. In addition to the above adverse reactions, the following adverse reactions have been reported with isotretinoin: allergic reactions, including vasculitis, systemic hypersensitivity, edema, lymphadenopathy, weight loss.

Cardiovas cular

The following adverse reactions have been reported with isotretinoin: vascular thrombotic disease, stroke, palpitation, tachycardia.

Endocrine/Metabolism and Nutritional

The following adverse reactions have been reported in a clinical trial conducted with ABSORICA and a generic product of Accutane[®] (isotretinoin): decreased appetite, weight fluctuation, hyperlipidaemia. In addition to the above adverse reactions, the following adverse reactions have been reported with isotretinoin: hypertriglyceridemia, alterations in blood sugar.

Gas trointes tinal

The following adverse reactions have been reported in a clinical trial conducted with ABSORICA and a generic product of Accutane[®] (isotretinoin): lip dry, chapped lips, cheilitis, nausea, constipation, diarrhea, abdominal pain, vomiting. In addition to the above adverse reactions, the following adverse reactions have been reported with isotretinoin: inflammatory bowel disease, hepatitis, pancreatitis, bleeding and inflammation of the gums, colitis, esophagitis/esophageal ulceration, ileitis, and other nonspecific gastrointestinal symptoms.

Hematologic

The following adverse reactions have been reported with isotretinoin: allergic reactions, anemia, thrombocytopenia, neutropenia, rare reports of agranulocytosis.

Infections and infestations

The following adverse reactions have been reported in a clinical trial conducted with ABSORICA and a generic product of Accutane[®] (isotretinoin): nasopharyngitis, hordeolum, upper respiratory tract infection. In addition to the above adverse reactions, the following adverse reaction has been reported with isotretinoin: infections (including disseminated herpes simplex).

Laboratory Abnormalities

The following changes in laboratory tests have been noted in a clinical trial conducted with ABSORICA and a generic product of Accutane[®] (isotretinoin): blood creatine phosphokinase (CPK) increased, blood triglycerides increased, alanine aminotransferase (SGPT) increased, aspartate aminotransferase (SGOT) increased, gamma-glutamyltransferase (GGTP) increased, blood cholesterol increased, low density lipoprotein (LDL) increased, white blood cell count decreased, blood alkaline phosphatase increased, blood bilirubin increased, blood glucose increased, high density lipopoprotein (HDL) decreased, bone mineral density decreased. In addition to the above adverse reactions, the following adverse reactions have been reported with isotretinoin: increased LDH, elevation of fasting blood sugar, hyperuricemia, decreases in red blood cell parameters, decreases in white blood cell counts (including severe neutropenia and rare reports of agranulocytosis), elevated sedimentation rates, elevated platelet counts, thrombocytopenia, white cells in the urine, proteinuria, microscopic or gross hematuria.

Musculoskeletal and Connective Tissue

The following adverse reactions have been reported in a clinical trial conducted with ABSORICA and a generic product of Accutane[®] (isotretinoin): decreases in bone mineral density, musculoskeletal symptoms (sometimes severe) including back pain, athralgia, musculoskeletal discomfort, musculoskeletal pain, neck pain, pain in extremity, myalgia, musculoskeletal stiffness [seeWarnings and Precautions (5.12)]. In addition to the above adverse reactions, the following adverse reactions have

been reported with isotretinoin: skeletal hyperostosis, calcification of tendons and ligaments, premature epiphyseal closure, tendonitis, arthritis, transient pain in the chest, and rare reports of rhabdomyolysis.

Neurological

The following adverse reactions have been reported in a clinical trial conducted with ABSORICA and a generic product of Accutane[®] (isotretinoin): headache, syncope. In addition to the above adverse reactions, other adverse reactions reported with isotretinoin include: pseudotumor cerebri, dizziness, drowsiness, lethargy, malaise, nervousness, paresthesias, seizures, stroke, weakness.

Psychiatric

The following adverse reactions have been reported in clinical trials conducted with ABSORICA and a generic product of Accutane[®] (isotretinoin): suicidal ideation, insomnia, anxiety, depression, irritability, panic attack, anger, euphoria, violent behaviors, emotional instability. In addition to the above adverse reactions, the following adverse reactions have been reported with isotretinoin: suicide attempts, suicide, aggression, psychosis and hallucination auditory. Of the patients reporting depression, some reported that the depression subsided with discontinuation of therapy and recurred with reinstitution of therapy.

Reproductive System

The following adverse reaction has been reported with isotretinoin: abnormal menses.

Respiratory

The following adverse reactions have been reported in a clinical trial conducted with ABSORICA and a generic product of Accutane[®] (isotretinoin): epistaxis, nasal dryness. In addition to the above adverse reactions, the following adverse reactions have been reported with isotretinoin: bronchospasms (with or without a history of asthma), respiratory infection, voice alteration.

Skin and Subcutaneous Tissue

The following adverse reactions have been reported in a clinical trial conducted with ABSORICA and a generic product of Accutane[®] (isotretinoin): dry skin, dermatitis, eczema, rash, dermatitis contact, alopecia, pruritus, sunburn, erythema. In addition to the above adverse reactions, the following adverse reactions have been reported with isotretinoin: acne fulminans, alopecia (which in some cases persists), bruising, dry nose, eruptive xanthomas, erythema multiforme, flushing, fragility of skin, hair abnormalities, hirsutism, hyperpigmentation and hypopigmentation, nail dystrophy, paronychia, peeling of palms and soles, photoallergic/photosensitizing reactions, pruritus, pyogenic granuloma, rash (including facial erythema, seborrhea, and eczema), Stevens-Johnson syndrome, sunburn susceptibility increased, sweating, toxic epidermal necrolysis, urticaria, vasculitis (including Wegener's granulomatosis), abnormal wound healing (delayed healing or exuberant granulation tissue with crusting).

Special Senses

Hearing: The following adverse reactions have been reported with isotretinoin: tinnitus and hearing impairment.

Ocular: The following adverse reactions have been reported in clinical trials conducted with ABSORICA and a generic product of Accutane[®] (isotretinoin): dry eye, visual acuity reduced, vision blurred, eye pruritis, eye irritation, asthenopia, decreased night vision, ocular hyperemia, increased lacrimation, and conjunctivitis. In addition to the above adverse reactions, the following adverse reactions have been reported with isotretinoin: corneal opacities, decreased night vision which may persist, cataracts, color vision disorder, conjunctivitis, eyelid inflammation, keratitis, optic neuritis, photobia, visual disturbances.

Renal and Urinary

The following adverse reactions have been reported in clinical trials conducted with isotretinoin:

glomerulonephritis, nonspecific urogenital findings.

7 DRUG INTERACTIONS

7.1 Vitamin A

ABSORICA is closely related to vitamin A. Therefore, the use of both vitamin A and ABSORICA at the same time may lead to vitamin A side effects. Patients should be advised against taking vitamin supplements containing Vitamin A to avoid additive toxic effects.

7.2 Tetracyclines

Concomitant treatment with ABSORICA and tetracyclines should be avoided because isotretinoin use has been associated with a number of cases of pseudotumor cerebri (benign intracranial hypertension), some of which involved concomitant use of tetracyclines.

7.3 Phenytoin

Isotretinoin has not been shown to alter the pharmacokinetics of phenytoin in a trial in seven healthy volunteers. These results are consistent with the in vitro finding that neither isotretinoin nor its metabolites induce or inhibit the activity of the CYP2C9 human hepatic P450 enzyme. Phenytoin is known to cause osteomalacia. No formal clinical trials have been conducted to assess if there is an interactive effect on bone loss between phenytoin and isotretinoin. Therefore, caution should be exercised when using these drugs together.

7.4 St. John's Wort

Isotretinoin use is associated with depression in some patients. Patients should be prospectively cautioned not to self-medicate with the herbal supplement St. John's Wort because a possible interaction has been suggested with hormonal contraceptives based on reports of breakthrough bleeding on oral contraceptives shortly after starting St. John's Wort. Pregnancies have been reported by users of combined hormonal contraceptives who also used some form of St. John's Wort.

7.5 Systemic Corticosteroids

Systemic corticosteroids are known to cause osteoporosis. No formal clinical trials have been conducted to assess if there is an interactive effect on bone loss between systemic corticosteroids and isotretinoin. Therefore, caution should be exercised when using these drugs together.

7.6 Norethindrone/ethinyl estradiol

In a trial of 31 premenopausal female patients with severe recalcitrant nodular acne receiving Norethindrone/ethinyl estradiol as an oral contraceptive agent, isotretinoin at the recommended dose of 1 mg/kg/day, did not induce clinically relevant changes in the pharmacokinetics of ethinyl estradiol and norethindrone and in the serum levels of progesterone, follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Prescribers are advised to consult the package insert of medication administered concomitantly with hormonal contraceptives, since some medications may decrease the effectiveness of these birth control products.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X [see Contraindications (4) and Warnings and Precautions (5.1)].

Risk Summary

ABSORICA is contraindicated during pregnancy because isotretinoin can cause can cause fetal harm

when administered to a pregnant woman. There is an increased risk of major congenital malformations, spontaneous abortions, and premature births following isotretinoin exposure during pregnancy in humans. If this drug is used during pregnancy, or if the patient becomes pregnant while taking the drug, the patient should be apprised of the potential hazard to a fetus.

Clinical Considerations

If pregnancy does occur during treatment of a female patient who is taking ABSORICA, ABSORICA must be discontinued immediately and she should be referred to an obstetrician-gynecologist experienced in reproductive toxicity for further evaluation and counseling.

Human Data

Major congenital malformations that have been documented following isotretinoin exposure include malformations of the face, eyes, ears, skull, central nervous system, cardiovascular system, and thymus and parathyroid glands. External malformations include: skull; ear (including anotia, micropinna, small or absent external auditory canals); eye (including microphthalmia); facial dysmorphia and cleft palate. Internal abnormalities include: CNS (including cerebral and cerebellar malformations, hydrocephalus, microcephaly, cranial nerve deficit); cardiovascular; thymus gland; parathyroid hormone deficiency. In some cases death has occurred as a result of the malformations.

Isotretinoin is found in the semen of male patients taking isotretinoin, but the amount delivered to a female partner would be about one million times lower than an oral dose of 40 mg. While the no-effect limit for isotretinoin induced embryopathy is unknown and 20 years of post-marketing reports include four reports with isolated defects compatible with features of retinoid exposed fetuses, two of these reports were incomplete and two had other possible explanations for the defects observed.

Cases of IQ scores less than 85 with or without other abnormalities have been reported. An increased risk of spontaneous abortion and premature births have been documented with isotretinoin exposure during pregnancy.

8.3 Nursing Mothers

It is not known whether this drug is present in human milk. Because many drugs are present in human milk and because of the potential for serious adverse reactions in nursing infants from ABSORICA, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The use of ABSORICA in pediatric patients less than 12 years of age has not been studied. The use of ABSORICA for the treatment of severe recalcitrant nodular acne in pediatric patients ages 12 to 17 years should be given careful consideration, especially for those patients where a known metabolic or structural bone disease exists [see Warnings and Precautions (5.12)]. Use of ABSORICA in this age group for severe recalcitrant nodular acne is supported by evidence from a clinical trial of ABSORICA compared to a generic product of Accutane[®] (isotretinoin) in 397 pediatric patients (12 to 17 years). Results from this trial demonstrated that both ABSORICA and the other isotretinoin drug product, at a dose of 1 mg/kg/day given in two divided doses, was effective in treating severe recalcitrant nodular acne in pediatric patients.

In trials with isotretinoin, adverse reactions reported in pediatric patients were similar to those described in adults except for the increased incidence of back pain and arthralgia (both of which were sometimes severe) and myalgia in pediatric patients. In a trial of pediatric patients treated with isotretinoin, approximately 29% (104/358) developed back pain. Back pain was severe in 13.5% (14/104) of the cases and occurred at a higher frequency in female patients than male patients. Arthralgias were experienced in 22% (79/358) of pediatric patients. Arthralgias were severe in 7.6% (6/79) of patients. Appropriate evaluation of the musculoskeletal system should be done in patients who present with these symptoms during or after a course of ABSORICA. Consideration should be given to

discontinuation of ABSORICA if any significant abnormality is found.

The effect on bone mineral density (BMD) of a 20-week course of therapy with ABSORICA or a generic product of Accutane (isotretinoin) was evaluated in a double-blind, randomized clinical trial involving 396 adolescents with severe recalcitrant nodular acne (mean age 15.4, range 12-17, 80% males). Following 20 weeks of treatment, there were no statistically significant differences between the treatment groups. The mean changes in BMD from baseline for the overall trial population were 1.8% for lumbar spine, -0.1% for total hip and -0.3% for femoral neck. Mean BMD Z-scores declined from baseline at each of these sites (-0.053, -0.109 and -0.104 respectively). Out of 306 adolescents, 27 (8.8%) had clinically significant BMD declines defined as \geq 4% lumbar spine or total hip, or \geq 5% femoral neck, including 2 subjects for lumbar spine, 17 for total hip and 20 for femoral neck. Repeat DXA scans within 2-3 months after the post treatment scan showed no recovery of BMD. Longer-term follow up at 4-11 months showed that 3 out of 7 patients had total hip and femoral neck BMD below pretreatment baseline, and 2 others did not show the increase in BMD above baseline expected in this adolescent population. The significance of these changes in regard to long-term bone health and future fracture risk is unknown [see Warnings and Precautions (5.12)].

In an open-label clinical trial (N=217) of a single course of therapy with isotretinoin for adolescents with severe recalcitrant nodular acne, bone density measurements at several skeletal sites were not significantly decreased (lumbar spine change >-4% and total hip change >-5%) or were increased in the majority of patients. One patient had a decrease in lumbar spine bone mineral density >4% based on unadjusted data. Sixteen (7.9%) patients had decreases in lumbar spine bone mineral density >4%, and all the other patients (92%) did not have significant decreases or had increases (adjusted for body mass index). Nine patients (4.5%) had a decrease in total hip bone mineral density >5% based on unadjusted data. Twenty-one (10.6%) patients had decreases in total hip bone mineral density >5%, and all the other patients (89%) did not have significant decreases or had increases (adjusted for body mass index). Follow-up trials performed in 8 of the patients with decreased bone mineral density for up to 11 months thereafter demonstrated increasing bone density in 5 patients at the lumbar spine, while the other 3 patients had lumbar spine bone density measurements below baseline values. Total hip bone mineral densities remained below baseline (range -1.6% to -7.6%) in 5 of 8 patients (62.5%).

In a separate open-label extension trial of 10 patients, ages 13 to 18 years, who started a second course of isotretinoin 4 months after the first course, two patients showed a decrease in mean lumbar spine bone mineral density up to 3.25%.

There are spontaneous literature reports of premature epiphyseal closure in acne patients receiving recommended doses of isotretinoin. The effect of multiple courses of isotretinoin on epiphyseal closure is unknown. In a 20-week clinical trial that included 289 adolescents who had hand radiographs taken to assess bone age, a total of 9 patients had bone age changes that were clinically significant and for which a drug-related effect cannot be excluded [see Warnings and Precautions (5.12)].

8.5 Geriatric Use

Clinical trials of ABSORICA did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. Although reported clinical experience has not identified differences in responses between elderly and younger patients, effects of aging might be expected to increase some risks associated with ABSORICA therapy.

8.6 Females of Childbearing Potential

All females of childbearing potential must comply with the iPLEDGE program requirements [see *Warnings and Precautions* (5.2)].

Pregnancy Testing

ABSORICA must only be prescribed to female patients who are known not to be pregnant as confirmed by a negative CLIA-certified laboratory conducted pregnancy test. Female patients of childbearing potential must have had two negative urine or serum pregnancy tests with a sensitivity of at least 25

mIU/mL before receiving the initial ABSORICA prescription. The first test (a screening test) is obtained by the prescriber when the decision is made to pursue qualification of the patient for ABSORICA. The second pregnancy test (a confirmation test) must be done in a CLIA-certified laboratory. The interval between the two tests must be at least 19 days.

- For patients with regular menstrual cycles, perform the second pregnancy test during the first 5 days of the menstrual period immediately preceding the beginning of ABSORICA therapy and after the patient has used 2 forms of contraception for 1 month.
- For patients with amenorrhea, irregular cycles, or using a contraceptive method that precludes withdrawal bleeding, perform the second pregnancy test immediately preceding the beginning of ABSORICA therapy and after the patient has used 2 forms of contraception for 1 month.

Each month of continued ABSORICA therapy, patients must have a negative result from a urine or serum pregnancy test. A pregnancy test must be repeated each month, in a CLIA-certified laboratory, prior to the female patient receiving each prescription. A pregnancy test must also be completed at the end of the entire course of isotretinoin therapy and 1 month after the discontinuation of isotretinoin.

Contraception

Females of childbearing potential must use 2 forms of effective contraception simultaneously, at least 1 of which must be a primary form, unless the patient commits to continuous abstinence from heterosexual contact, or the patient has undergone a hysterectomy or bilateral oophorectomy, or has been medically confirmed to be post-menopausal. Patients must use 2 forms of effective contraception for at least 1 month prior to initiation of ABSORICA therapy, during ABSORICA therapy, and for 1 month after discontinuing ABSORICA therapy. Micro-dosed progesterone preparations ("minipills" that do not contain an estrogen) are an inadequate method of contraception during isotretinoin therapy [seeWarnings and Precautions (5.3)].

Effective forms of contraception include both primary and secondary forms of contraception:

Primary forms	Secondary forms	
 Tubal sterilization Partner's vasectomy Intrauterine device Hormonal (combination oral contraceptives, transdermal patch, injectables, implantables, or vaginal ring) 	Barrier: • male latex condom with or without spermicide • diaphragm with spermicide • cervical cap with spermicide Other: • Vaginal sponge (contains spermicide)	
	spermicide)	

Any birth control method can fail. There have been reports of pregnancy from female patients who have used combination oral contraceptives, as well as transdermal patch/injectable/implantable/vaginal ring hormonal birth control products; these pregnancies occurred while taking isotretinoin. These reports are more frequent for female patients who use only a single method of contraception. Therefore, it is critically important for female patients of childbearing potential use 2 effective forms of contraception simultaneously.

Using two forms of contraception simultaneously substantially reduces the chances that a female will become pregnant over the risk of pregnancy with either form alone. A drug interaction that decreases effectiveness of hormonal contraceptives has not been entirely ruled out for isotretinoin. Although

hormonal contraceptives are highly effective, prescribers are advised to consult the package insert of any medication administered concomitantly with hormonal contraceptives, since some medications may decrease the effectiveness of these birth control products.

Patients should be prospectively cautioned not to self-medicate with the herbal supplement St. John's Wort because a possible interaction has been suggested with hormonal contraceptives based on reports of breakthrough bleeding on oral contraceptives shortly after starting St. John's Wort. Pregnancies have been reported by users of combined hormonal contraceptives who also used some form of St. John's Wort [see Drug Interactions (7.4)].

If the patient has unprotected heterosexual intercourse at any time 1 month before, during, or 1 month after therapy, she must:

- Stop taking ABSORICA immediately, if on therapy
- Have a pregnancy test at least 19 days after the last act of unprotected heterosexual intercourse
- Start using 2 forms of effective contraception simultaneously again for 1 month before resuming ABSORICA therapy
- Have a second pregnancy test after using 2 forms of effective contraception for 1 month as described above depending on whether she has regular menses or not.

If a pregnancy does occur during ABSORICA treatment, ABSORICA must be discontinued immediately. The patient should be referred to an Obstetrician-Gynecologist experienced in reproductive toxicity for further evaluation and counseling. Any suspected fetal exposure during or 1 month after ABSORICA therapy must be reported immediately to the FDA via the MedWatch number 1-800-FDA-1088 and also to the iPLEDGE pregnancy registry at 1-866-495-0654 or via the internet (www.ipledgeprogram.com) [see Warnings and Precautions (5.2)].

10 OVERDOSAGE

In humans, overdosage has been associated with vomiting, facial flushing, cheilosis, abdominal pain, headache, dizziness, and ataxia. These symptoms quickly resolve without apparent residual effects.

ABSORICA causes serious birth defects at any dosage (see Boxed CONTRAINDICATIONS AND WARNINGS). Female patients of childbearing potential who present with ABSORICA overdose must be evaluated for pregnancy. Patients who are pregnant should receive counseling about the risks to the fetus, as described in the Boxed CONTRAINDICATIONS AND WARNINGS. Non-pregnant patients must be warned to avoid pregnancy for at least one month and receive contraceptive counseling as described in *Warnings and Precautions* (5). Educational materials for such patients can be obtained by calling the manufacturer. Because an overdose would be expected to result in higher levels of isotretinoin in semen than found during a normal treatment course, male patients should use a condom, or avoid reproductive sexual activity with a female patient who is or might become pregnant, for 1 month after the overdose. All patients with ABSORICA overdose should not donate blood for at least 1 month.

11 DESCRIPTION

ABSORICA (isotretinoin) Capsules contain 10 mg, 20 mg, 25 mg, 30 mg, 35 mg or 40 mg of isotretinoin (a retinoid) in hard gelatin capsules for oral administration. In addition to the active ingredient, isotretinoin, each capsule contains the following inactive ingredients: propyl gallate, sorbitan monooleate, soybean oil and stearoyl polyoxylglycerides. The gelatin capsules contain the following dye systems:

- 10 mg iron oxide (yellow) and titanium dioxide;
- 20 mg iron oxide (red), and titanium dioxide;
- 25 mg FD&C Blue #1, FD&C Yellow #5, FD&C Yellow #6 and titanium dioxide;

- 30 mg iron oxide (black, red and yellow) and titanium dioxide;
- 35 mg FD&C Blue #2, iron oxide (black, red and yellow) and titanium dioxide;
- 40 mg iron oxide (black, red and yellow) and titanium dioxide.

Chemically, isotretinoin is 13-*cis*-retinoic acid and is related to both retinoic acid and retinol (vitamin A). It is a yellow to orange crystalline powder with a molecular weight of 300.44. It is practically insoluble in water, soluble in chloroform and sparingly soluble in alcohol and in isopropyl alcohol. The structural formula is:

Meets USP Dissolution Test 3.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

ABSORICA is a retinoid, which when administered in pharmacologic dosages of 0.5 to 1 mg/kg/day, inhibits sebaceous gland function and keratinization. Clinical improvement in nodular acne patients occurs in association with a reduction in sebum secretion. The decrease in sebum secretion is temporary and is related to the dose and duration of treatment with isotretinoin and reflects a reduction in sebaceous gland size and an inhibition of sebaceous gland differentiation. The exact mechanism of action of ABSORICA is unknown.

12.2 Pharmacodynamics

The pharmacodynamics of ABSORICA are unknown.

12.3 Pharmacokinetics

Absorption

Due to its high lipophilicity, oral absorption of isotretinoin is enhanced when given with a high-fat meal. ABSORICA is bioequivalent to $Accutane^{\$}$ (isotretinoin) capsule when both drugs are taken with a high-fat meal. ABSORICA is more bioavailable than $Accutane^{\$}$ (isotretinoin) capsules when both drugs are taken fasted; the AUC_{0-t} of ABSORICA is approximately 83% greater than that of $Accutane^{\$}$. ABSORICA is therefore not interchangeable with generic products of $Accutane^{\$}$.

A single dose two-way crossover pharmacokinetic trial was conducted in 14 healthy adult male subjects comparing ABSORICA 40 mg (1 x 40 mg capsules), dosed under fasted and fed conditions. Under fed conditions after a high-fat meal, it was observed that the mean AUC_{0-t} and C_{max} were approximately 50% and 26% higher, than that observed under fasting conditions (Table 2). The observed elimination half-life ($T_{1/2}$) was slightly lower in the fed state versus fasted. The time to peak concentration (T_{max}) increased with food and this may be related to a longer absorption phase.

Table 2: Pharmacokinetic parameters of ABSORICA mean (%CV) following administration of 40 mg strength, N=14

ABSORICA¶ (1 x 40 mg capsules)	AUC _{0-t} (ng x hr/mL)	C _{max} (ng/mL)	T _{max} (hr)	T _{1/2} (hr)
Fed	6095 (26 %)	395 (39 %)	6.4 (47 %)	22 (25 %)
Fasted	4055 (20 %)	314 (26 %)	2.9 (34 %)	24 (28 %)

Published clinical literature has shown that there is no difference in the pharmacokinetics of isotretinoin between patients with nodular acne and healthy subjects with normal skin.

Distribution

Isotretinoin is more than 99.9% bound to plasma proteins, primarily albumin.

Metabolis m

Following oral administration of isotretinoin, at least three metabolites have been identified in human plasma: 4-oxo-isotretinoin, retinoic acid (tretinoin), and 4-oxo-retinoic acid (4-oxo-tretinoin). Retinoic acid and 13-cis-retinoic acid are geometric isomers and show reversible interconversion. The administration of one isomer will give rise to the other. Isotretinoin is also irreversibly oxidized to 4-oxo-isotretinoin, which forms its geometric isomer 4-oxo-tretinoin.

After a single 40 mg oral dose of ABSORICA to 57 healthy adult subjects, concurrent administration of food increased the extent of formation of all metabolites in plasma when compared to the extent of formation under fasted conditions.

All of these metabolites possess retinoid activity that is in some in vitro models more than that of the parent isotretinoin. However, the clinical significance of these models is unknown.

In vitro studies indicate that the primary P450 isoforms involved in isotretinoin metabolism are 2C8, 2C9, 3A4, and 2B6. Isotretinoin and its metabolites are further metabolized into conjugates, which are then excreted in urine and feces.

Elimination

Following oral administration of an 80 mg dose of 14C-isotretinoin as a liquid suspension, 14C-activity in blood declined with a half-life of 90 hours. The metabolites of isotretinoin and any conjugates are ultimately excreted in the feces and urine in relatively equal amounts (total of 65% to 83%).

After a single 40 mg (2 x 20 mg) oral dose of ABSORICA to 57 healthy adult subjects under fed conditions, the mean \pm SD elimination half-lives ($T_{1/2}$) of isotretinoin and 4-*oxo*-isotretinoin under fed states were 18 hours and 38 hours, respectively.

Special Patient Populations

The pharmacokinetics of isotretinoin were evaluated after single and multiple doses in 38 pediatric patients (12 to 15 years) and 19 adult patients (\geq 18 years) who received isotretinoin for the treatment of severe recalcitrant nodular acne. In both age groups, 4-oxo-isotretinoin was the major metabolite; tretinoin and 4-oxo-tretinoin were also observed. There were no statistically significant differences in the pharmacokinetics of isotretinoin between pediatric and adult patients.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis and Impairment of Fertility

In male and female Fischer 344 rats given oral isotretinoin at dosages of 8 or 32 mg/kg/day (1.3 to 5.3 times the recommended clinical dose of 1 mg/kg/day, respectively, after normalization for total body surface area) for greater than 18 months, there was a dose-related increased incidence of pheochromocytoma relative to controls. The incidence of adrenal medullary hyperplasia was also increased at the higher dosage in both sexes. The relatively high level of spontaneous pheochromocytomas occurring in the male Fischer 344 rat makes it an equivocal model for study of this tumor; therefore, the relevance of this tumor to the human population is uncertain.

The Ames test was conducted with isotretinoin in two laboratories. The results of the tests in one laboratory were negative while in the second laboratory a weakly positive response (less than 1.6 x background) was noted in *S. typhimurium* TA100 when the assay was conducted with metabolic

activation. No dose response effect was seen and all other strains were negative. Additionally, other tests designed to assess genotoxicity (Chinese hamster cell assay, mouse micronucleus test, *S. cerevisiae* D7 assay, in vitro clastogenesis assay with human-derived lymphocytes, and unscheduled DNA synthesis assay) were all negative.

In rats, no adverse effects on gonadal function, fertility, conception rate, gestation or parturition were observed at oral dosages of isotretinoin of 2, 8, or 32 mg/kg/day (0.3, 1.3, or 5.3 times the recommended clinical dose of 1 mg/kg/day, respectively, after normalization for total body surface area).

In dogs, testicular atrophy was noted after treatment with oral isotretinoin for approximately 30 weeks at dosages of 20 or 60 mg/kg/day (10 or 30 times the recommended clinical dose of 1 mg/kg/day, respectively, after normalization for total body surface area). In general, there was microscopic evidence for appreciable depression of spermatogenesis but some sperm were observed in all testes examined and in no instance were completely atrophic tubules seen.

In trials of 66 men, 30 of whom were patients with nodular acne under treatment with oral isotretinoin, no significant changes were noted in the count or motility of spermatozoa in the ejaculate. In a study of 50 men (ages 17 to 32 years) receiving isotretinoin therapy for nodular acne, no significant effects were seen on ejaculate volume, sperm count, total sperm motility, morphology or seminal plasma fructose.

13.2 Animal Toxicology

In rats given 8 or 32 mg/kg/day of isotretinoin (1.3 to 5.3 times the recommended clinical dose of 1 mg/kg/day after normalization for total body surface area) for 18 months or longer, the incidences of focal calcification, fibrosis and inflammation of the myocardium, calcification of coronary, pulmonary and mesenteric arteries, and metastatic calcification of the gastric mucosa were greater than in control rats of similar age. Focal endocardial and myocardial calcifications associated with calcification of the coronary arteries were observed in two dogs after approximately 6 to 7 months of treatment with isotretinoin at a dosage of 60 to 120 mg/kg/day (30 to 60 times the recommended clinical dose of 1 mg/kg/day, respectively, after normalization for total body surface area).

14 CLINICAL STUDIES

A double-blind, randomized, parallel group trial (Study 1) was conducted in patients with severe recalcitrant nodular acne to evaluate the efficacy and safety of ABSORICA compared to a generic product of Accutane[®] under fed conditions. Enrolled patients had a weight of 40 to 110 kg with at least 10 nodular lesions on the face and/or trunk. A total of 925 patients were randomized 1:1 to receive ABSORICA or a generic product of Accutane[®] (isotretinoin). Study patients ranged from 12 to 54 years of age, were approximately 60% male, 40% female, and were 87% White, 4% Black, 6% Asian, and 3% Other. Patients were treated an initial dose of 0.5 mg/kg/day in two divided doses for the first 4 weeks followed by 1 mg/kg/day in two divided doses for the following 16 weeks.

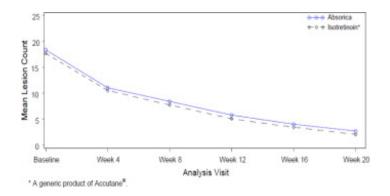
Change from Baseline to Week 20 in total nodular lesion count and proportion of patients with at least a 90% reduction in total nodular lesion count from Baseline to Week 20 are presented in Table 3. Total nodular lesion counts by visit are presented in Figure 1.

Table 3: Efficacy Results at Week 20 (Study 1)

	ABSORICA¶ N=464	Isotretinoin* N=461
Nodular Lesions		
Mean Baseline Count	18.4	17.7
Mean Reduction	-15.68	-15.62
Patients Achieving 90% Reduction	324 (70%)	344 (75%)
*A generic product of Accutane®		

*A generic product of Accutane®

Figure 1: Total Nodular (Facial and Truncal) Lesion Count by Visit in Study 1



16 HOW SUPPLIED/STORAGE AND HANDLING

ABSORICA (isotretinoin) Capsules are supplied as follows:

- **10 mg:** Dark yellow, opaque, capsule imprinted with black ink "**G 240**" on cap and "**10**" on the body

 Box of 30 capsules (3 x 10 Prescription Packs): NDC 10631-115-31
- **20 mg:** Red, opaque, capsule imprinted with black ink "**G 241**" on cap and "**20**" on the body Box of 30 capsules (3 x 10 Prescription Packs): NDC 10631-116-31
- **25 mg:** Green, opaque, capsule imprinted with white ink "**G 342**" on cap and "**25**" on the body Box of 30 capsules (3 x 10 Prescription Packs): NDC 10631-133-31
- **30 mg:** Brown, opaque, capsule imprinted with white ink "**G 242**" on cap and "**30**" on the body Box of 30 capsules (3 x 10 Prescription Packs): NDC 10631-117-31
- **35 mg:** Dark blue, opaque, capsule imprinted with white ink "**G 343**" on cap and "**35**" on the body Box of 30 capsules (3 x 10 Prescription Packs): NDC 10631-134-31
- **40 mg:** Brown and red, capsule imprinted with white ink "**G 325**" on cap and "**40**" on the body Box of 30 capsules (3 x 10 Prescription Packs): NDC10631-118-31

Storage and Handling

Store at 20° C - 25° C (68° F - 77° F), excursion permitted between 15° C - 30° C (59° F - 86° F) [see USP controlled room temperature]. Protect from light.

17 PATIENT COUNSELING INFORMATION

Advise the patient that ABSORICA is only available through a restricted program called iPLEDGE.

• As a component of the iPLEDGE program, prescribers must instruct patients to read the Medication Guide, the iPLEDGE program patient educational booklets, and watch the DVD with the following videos — "Be Prepared, Be Protected" and "Be Aware: The Risk of Pregnancy While on Isotretinoin". The DVD includes information about contraception, the most common reasons that contraception fails, and the importance of using 2 forms of effective contraception when taking teratogenic drugs and comprehensive information about types of potential birth

- defects which could occur if a female patient who is pregnant takes ABSORICA at any time during pregnancy.
- Male patients and Female patients not of childbearing potential must understand the risks and benefits of ABSORICA, comply with the REMS requirements described in the booklet entitled *The iPLEDGE Program Guide to Isotretinoin for Male Patients and Female Patients Who Cannot Get Pregnant*, and sign a Patient Information/Informed Consent form.
- Female patients of childbearing potential must be instructed that they must not be pregnant when ABSORICA therapy is initiated or plan to become pregnant while receiving ABSORICA therapy. Additionally, they must use 2 forms of effective contraception simultaneously for 1 month before starting ABSORICA, while taking ABSORICA, and for 1 month after ABSORICA has been stopped, unless they commit to continuous abstinence from heterosexual intercourse. They should also sign a Patient Information/Informed Consent form and Patient Information/Informed Consent About Birth Defects (for female patients who can get pregnant) form prior to beginning ABSORICA therapy. Female patients should be seen by their prescribers monthly and have a urine or serum pregnancy test, in a CLIA-certified laboratory, performed each month during treatment to confirm negative pregnancy status before another ABSORICA prescription is written. Additionally, a pregnancy test must be completed at the end of the entire course of ABSORICA therapy and 1 month after discontinuation of therapy.
- Advise the patient that isotretinoin is found in the semen of male patients taking isotretinoin, but the amount delivered to a female partner would be about one million times lower than an oral dose of 40 mg. While the no-effect limit for isotretinoin induced embryopathy is unknown, 20 years of post-marketing reports include four with isolated defects compatible with features of retinoid exposed fetuses; however two of these reports were incomplete and two had other possible explanations for the defects observed.
- Advise the patient that ABSORICA is available only from pharmacies that are certified in the iPLEDGE program, and provide them with the telephone number (1-866-495-0654) and website (www.ipledgeprogram.com) for information on how to obtain.
- Advise patients that they may be requested to participate in a survey to evaluate the effectiveness of the iPLEDGE program.
- Prescribers should be alert to the warning signs of psychiatric disorders to guide patients to receive the help they need. Therefore, prior to initiation of ABSORICA treatment, patients and family members should be asked about any history of psychiatric disorder, and at each visit during treatment patients should be assessed for symptoms of depression, mood disturbance, psychosis, or aggression to determine if further evaluation may be necessary. Inform patients that **symptoms** of depression include sad mood, hopelessness, feelings of guilt, worthlessness or helplessness, loss of pleasure or interest in activities, fatigue, difficulty concentrating, change in sleep pattern, change in weight or appetite, suicidal thoughts or attempts, restlessness, irritability, acting on dangerous impulses, and persistent physical symptoms **unresponsive to treatment**. Patients should stop treatment and the patient or a family member should promptly contact their prescriber if the patient develops depression, mood disturbance, psychosis, or aggression, without waiting until the next visit. Discontinuation of ABSORICA treatment may be insufficient; further evaluation may be necessary. While such monitoring may be helpful, it may not detect all patients at risk. Patients may report mental health problems or family history of psychiatric disorders. These reports should be discussed with the patient and/or the patient's family. A referral to a mental health professional may be necessary. The physician should consider whether ABSORICA therapy is appropriate in this setting; for some patients the risks may outweigh the benefits of ABSORICA therapy.
- Patients must be informed that some patients, while taking isotretinoin or soon after stopping isotretinoin, have become depressed or developed other serious mental problems. Symptoms of depression include sad, "anxious" or empty mood, irritability, acting on dangerous impulses, anger, loss of pleasure or interest in social or sports activities, sleeping too much or too little, changes in weight or appetite, school or work performance going down, or trouble concentrating.

Some patients taking isotretinoin have had thoughts about hurting themselves or putting an end to their own lives (suicidal thoughts), some have tried to end their own lives, and some have ended their own lives. There were reports that some of these people did not appear depressed. There have been reports of patients on isotretinoin becoming aggressive or violent. There have also been reports of psychotic symptoms, which indicate a loss of contact with reality. Psychotic symptoms include feelings of suspiciousness toward others, strange beliefs, hearing voices or other noises without an obvious source, and seeing unusual objects or people with no explanation. No one knows if isotretinoin caused these behaviors and symptoms or if they would have happened even if the person did not take isotretinoin. If any of these behaviors or symptoms occur, the patient should stop treatment and the patient or family member should contact the prescriber promptly without waiting until the next visit [see Warnings and Precautions (5.4)]. Some people have had other signs of depression while taking isotretinoin.

- Patients must be informed that they must not share ABSORICA with anyone else because of the risk of birth defects and other serious adverse reactions.
- Patients must be informed not to donate blood during therapy and for 1 month following discontinuation of the drug because the blood might be given to a pregnant female patient whose fetus must not be exposed to ABSORICA.
- ABSORICA may be taken without regard to meals [see Dosage and Administration (2.1)]. To
 decrease the risk of esophageal irritation, patients should swallow the capsules with a full glass
 of liquid.
- Patients should be informed that inflammatory bowel disease (including regional ileitis) may occur without a prior history of intestinal disorders. In rare instances, symptoms have been reported to persist after treatment has stopped. Patients should be informed that if they experience abdominal pain, rectal bleeding or severe diarrhea, they should discontinue ABSORICA immediately.
- Patients should be informed that transient exacerbation (flare) of acne has been seen, generally during the initial period of therapy.
- Wax epilation and skin resurfacing procedures (such as dermabrasion, laser) should be avoided during ABSORICA therapy and for at least 6 months thereafter due to the possibility of scarring.
- Patients should be advised to avoid prolonged exposure to UV rays or sunlight.
- Patients should be informed that they may experience dry eye, corneal opacities, and decreased night vision. Contact lens wearers may experience decreased tolerance to contact lenses during and after therapy.
- Patients should be informed that 16% of patients treated with isotretinoin in a clinical trial developed musculoskeletal symptoms (including arthralgia) during treatment. In general, these symptoms were mild to moderate, but occasionally required discontinuation of the drug. Transient pain in the chest has been reported less frequently. In the clinical trial, these symptoms generally cleared rapidly after discontinuation of therapy, but in some cases persisted.
- There have been rare postmarketing reports of rhabdomyolysis, some associated with strenuous physical activity.
- Pediatric patients and their caregivers should be informed that approximately 17% to 29% of pediatric patients treated with isotretinoin developed back pain. In a clinical trial, back pain was severe in 13.5% of the cases and occurred at a higher frequency in female patients than male patients. Arthralgias were experienced in 22% (79/358) of pediatric patients. Arthralgias were severe in 7.6% (6/79) of patients. Appropriate evaluation of the musculoskeletal system should be done in patients who present with these symptoms during or after a course of treatment. Consideration should be given to discontinuation of isotretinoin if any significant abnormality is found.
- Neutropenia and rare cases of agranulocytosis have been reported in patients treated with isotretinoin. ABSORICA should be discontinued if clinically significant decreases in white cell counts occur.
- Patients should be advised that severe skin reactions (Stevens-Johnson syndrome and toxic

- epidermal necrolysis) have been reported in post marketing data in patients treated with isotretinoin. Treatment with ABSORICA should be discontinued if clinically significant skin reactions occur.
- Adolescent patients who participate in sports with repetitive impact should be informed that isotretinoin use may increase their risk of spondylolisthesis or hip growth plate injuries. There are spontaneous reports of fractures and/or delayed healing in patients while on therapy with isotretinoin or following cessation of therapy with isotretinoin while involved in these activities [see Warnings and Precautions (5.12)].

MEDICATION GUIDE

ABSORICA® (AB-SORE-I-KAH) (Is otretino in Capsules)

Read the Medication Guide that comes with ABSORICA before you start taking it and each time you get a prescription. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment.

What is the most important information I should know about ABSORICA?

- ABSORICA is used to treat a type of severe acne (nodular acne) that has not been helped by other treatments, including antibiotics.
- Because ABSORICA can cause birth defects, ABSORICA is only for patients who can understand
 and agree to carry out all of the instructions in the iPLEDGE program.
- ABSORICA may cause serious mental health problems.
- 1. Birth defects (deformed babies), loss of a baby before birth (miscarriage), death of the baby, and early (premature) births. Female patients who are pregnant or who plan to become pregnant must not take ABSORICA. Female patients must not get pregnant:
 - for 1 month before starting ABSORICA
 - while taking ABSORICA
 - for 1 month after stopping ABSORICA.

Ifyou get pregnant while taking ABSORICA, stop taking it right away and call your doctor. Doctors and patients should report all cases of pregnancy to:

- FDA MedWatch at 1-800-FDA-1088, and
- the iPLEDGE pregnancy registry at 1-866-495-0654
- **2. Serious mental health problems.** ABSORICA may cause:
 - depression
 - **psychosis** (seeing or hearing things that are not real)
 - **suicide**. Some patients taking ABSORICA have had thoughts about hurting themselves or putting an end to their own lives (suicidal thoughts). Some people tried to end their own lives. And some people have ended their own lives.

Stop ABSORICA and call your doctor right away if you or a family member notices that you have any of the following signs and symptoms of depression or psychosis:

- start to feel sad or have crying spells
- lose interest in activities you once enjoyed

- sleep too much or have trouble sleeping
- become more irritable, angry, or aggressive than usual (for example, temper outbursts, thoughts of violence)
- have a change in your appetite or body weight
- have trouble concentrating
- withdraw from your friends or family
- feel like you have no energy
- have feelings of worthlessness or guilt
- start having thoughts about hurting yourself or taking your own life (suicidal thoughts)
- start acting on dangerous impulses
- start seeing or hearing things that are not real

After stopping ABSORICA, you may also need follow-up mental health care if you had any of these symptoms.

What is ABSORICA?

ABSORICA is a medicine taken by mouth to treat the most severe form of acne (nodular acne) that cannot be cleared up by any other acne treatments, including antibiotics. ABSORICA can cause serious side effects (see "What is the most important information I should know about ABSORICA?"). ABSORICA can only be:

- prescribed by doctors that are registered in the iPLEDGE program
- dispensed by a pharmacy that is registered with the iPLEDGE program
- given to patients who are registered in the iPLEDGE program and agree to do everything required in the program

What is severe nodular acne?

Severe nodular acne is when many red, swollen, tender lumps form in the skin. These can be the size of pencil erasers or larger. If untreated, nodular acne can lead to permanent scars.

Who should not take ABSORICA?

- Do not take ABSORICA if you are pregnant, plan to become pregnant, or become pregnant during ABSORICA treatment. ABSORICA causes severe birth defects. See "What is the most important information I should know about ABSORICA?"
- **Do not take ABSORICA if you are allergic to anything in it.** See the end of this Medication Guide for a complete list of ingredients in ABSORICA.

What should I tell my doctor before taking ABSORICA?

Tell your doctor if you or a family member has any of the following health conditions:

- mental problems
- asthma
- liver disease
- diabetes
- heart disease
- bone loss (osteoporosis) or weak bones
- an eating problem called anorexia nervosa (where people eat too little)
- food or medicine allergies

Tell your doctor if you are pregnant or breast-feeding. ABSORICA must not be used by women who are pregnant or breast-feeding.

Tell your doctor about all of the medicines you take including prescription and non-prescription medicines, vitamins and herbal supplements. ABSORICA and certain other medicines can interact with each other, sometimes causing serious side effects. Especially tell your doctor if you take:

- **Vitamin A supplements**. Vitamin A in high doses has many of the same side effects as ABSORICA. Taking both together may increase your chance of getting side effects.
- **Tetracycline antibiotics**. Tetracycline antibiotics taken with ABSORICA can increase the chances of getting increased pressure in the brain.
- **Progestin-only birth control pills (mini-pills)**. They may not work while you take ABSORICA. Ask your doctor or pharmacist if you are not sure what type you are using.
- **Dilantin (phenytoin)**. This medicine taken with ABSORICA may weaken your bones.
- **Corticos teroid medicines**. These medicines taken with ABSORICA may weaken your bones.
- **St. John's Wort**. This herbal supplement may make birth control pills work less effectively.

These medicines should not be used with ABSORICA unless your doctor tells you it is okay.

Know the medicines you take. Keep a list of them to show to your doctor and pharmacist. Do not take any new medicine without talking with your doctor.

How should I take ABSORICA?

- You must take ABSORICA exactly as prescribed. You must also follow all the instructions of the iPLEDGE program. Before prescribing ABSORICA, your doctor will:
 - explain the iPLEDGE program to you
 - have you sign the Patient Information/Informed Consent form (for all patients). Female patients who can get pregnant must also sign another consent form.

You will not be prescribed ABSORICA if you cannot agree to or follow all the instructions of the iPLEDGE program.

- You will get no more than a 30-day supply of ABSORICA at a time. This is to make sure you are following the ABSORICA iPLEDGE program. You should talk with your doctor each month about side effects.
- The amount of ABSORICA you take has been specially chosen for you. It is based on your body weight, and may change during treatment.
- Take ABSORICA 2 times a day without regard to meals, unless your doctor tells you otherwise. **Swallow your ABSORICA capsules whole with a full glass of liquid. Do not chew or suck on the capsule.** ABSORICA can hurt the tube that connects your mouth to your stomach (esophagus) if it is not swallowed whole.
- If you miss a dose, just skip that dose. Do **not** take two doses at the same time.
- If you take too much ABSORICA or overdose, call your doctor or poison control center right away.
- Your acne may get worse when you first start taking ABSORICA. This should last only a short while. Talk with your doctor if this is a problem for you.
- You must return to your doctor as directed to make sure you don't have signs of serious side effects. Your doctor may do blood tests to check for serious side effects from ABSORICA. Female patients who can get pregnant will get a pregnancy test each month.
- Female patients who can get pregnant must agree to use two separate forms of effective birth

control at the same time one month before, while taking, and for one month after taking ABSORICA. **You must access the iPLEDGE system to answer questions about the program requirements and to enter your two chosen forms of birth control.** To access the iPLEDGE system, go to *www.ipledgeprogram.com* or call 1-866-495-0654.

You must talk about effective birth control methods with your doctor or go for a free visit to talk about birth control with another doctor or family planning expert. Your doctor can arrange this <u>free</u> visit, which will be paid for by the company that makes ABSORICA.

If you have sex at any time without using two forms of effective birth control, get pregnant, or miss your expected period, stop using ABSORICA and call your doctor right away.

What should I avoid while taking ABSORICA?

- **Do not get pregnant** while taking ABSORICA and for one month after stopping ABSORICA. See "What is the most important information I should know about ABSORICA?"
- **Do not breast-feed** while taking ABSORICA and for one month after stopping ABSORICA. We do not know if ABSORICA can pass through your milk and harm the baby.
- **Do not give blood** while you take ABSORICA and for one month after stopping ABSORICA. If someone who is pregnant gets your donated blood, her baby may be exposed to ABSORICA and may be born with birth defects.
- **Do not take other medicines or herbal products** with ABSORICA unless you talk to your doctor. See **"What should I tell my doctor before taking ABSORICA?"**
- **Do not drive at night until you know if ABSORICA has affected your vision.** ABSORICA may decrease your ability to see in the dark.
- Do not have cosmetic procedures to smooth your skin, including waxing, dermabrasion, or laser procedures, while you are using ABSORICA and for at least 6 months after you stop. ABSORICA can increase your chance of scarring from these procedures. Check with your doctor for advice about when you can have cosmetic procedures.
- **Avoid sunlight and ultraviolet lights** as much as possible. Tanning machines use ultraviolet lights. ABSORICA may make your skin more sensitive to light.

Do not share ABSORICA with other people. It can cause birth defects and other serious health problems.

What are the possible side effects of ABSORICA?

- ABSORICA can cause birth defects (deformed babies), loss of a baby before birth (miscarriage), death of the baby, and early (premature) births. See "What is the most important information I should know about ABSORICA?"
- ABSORICA may cause serious mental health problems. See "What is the most important information I should know about ABSORICA?"
- **serious brain problems.** ABSORICA can increase the pressure in your brain. This can lead to permanent loss of eyesight and, in rare cases, death. Stop taking ABSORICA and call your doctor right away if you get any of these signs of increased brain pressure:
 - bad headache
 - blurred vision
 - dizziness
 - nausea or vomiting
 - seizures (convulsions)

- stroke
- **skin problems.** Skin rash can occur in patients taking ABSORICA. In some patients a rash can be serious. Stop using ABSORICA and call your doctor right away if you develop conjunctivitis (red or inflamed eyes, like "pink eye"), a rash with a fever, blisters on legs, arms or face and/or sores in your mouth, throat, nose, eyes, or if your skin begins to peel.
- **stomach area (abdomen) problems.** Certain symptoms may mean that your internal organs are being damaged. These organs include the liver, pancreas, bowel (intestines), and esophagus (connection between mouth and stomach). If your organs are damaged, they may not get better even after you stop taking ABSORICA. Stop taking ABSORICA and call your doctor if you get:
 - severe stomach, chest or bowel pain
 - trouble swallowing or painful swallowing
 - new or worsening heartburn
 - diarrhea
 - rectal bleeding
 - yellowing of your skin or eyes
 - dark urine
- bone and muscle problems. ABSORICA may affect bones, muscles, and ligaments and cause
 pain in your joints or muscles. Tell your doctor if you plan hard physical activity during treatment
 with ABSORICA. Tell your doctor if you get:
 - back pain
 - joint pain
 - broken bone. Tell all healthcare providers that you take ABSORICA if you break a bone.

Stop ABSORICA and call your doctor right away if you have muscle weakness. Muscle weakness with or without pain can be a sign of serious muscle damage.

ABSORICA may stop long bone growth in teenagers who are still growing.

- **hearing problems.** Stop using ABSORICA and call your doctor if your hearing gets worse or if you have ringing in your ears. Your hearing loss may be permanent.
- **vision problems.** ABSORICA may affect your ability to see in the dark. This condition usually clears up after you stop taking ABSORICA, but it may be permanent. Other serious eye effects can occur. Stop taking ABSORICA and call your doctor right away if you have any problems with your vision or dryness of the eyes that is painful or constant. If you wear contact lenses, you may have trouble wearing them while taking ABSORICA and after treatment.
- **lipid (fats and choles terol in blood) problems.** ABSORICA can raise the level of fats and cholesterol in your blood. This can be a serious problem. Return to your doctor for blood tests to check your lipids and to get any needed treatment. These problems usually go away when ABSORICA treatment is finished.
- **serious allergic reactions.** Stop taking ABSORICA and get emergency care right away if you develop hives, a swollen face or mouth, or have trouble breathing. Stop taking ABSORICA and call your doctor if you get a fever, rash, or red patches or bruises on your legs.
- **blood sugar problems.** ABSORICA may cause blood sugar problems including diabetes. Tell your doctor if you are very thirsty or urinate a lot.
- decreased red and white blood cells. Call your doctor if you have trouble breathing, faint, or feel weak.

• **The common, less serious side effects of ABSORICA** are dry skin, chapped lips, dry eyes, and dry nose that may lead to nosebleeds. Call your doctor if you get any side effect that bothers you or that does not go away.

These are not all of the possible side effects with ABSORICA. Your doctor or pharmacist can give you more detailed information.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also report side effects to Ranbaxy Inc., the manufacturer of ABSORICA at 1-800-406-7984.

How should I store ABSORICA?

- Store ABSORICA at room temperature, 68° to 77° F (20° to 25° C). Protect from light.
- Keep ABSORICA and all medicines out of the reach of children.

General Information about ABSORICA

Medicines are sometimes prescribed for conditions that are not mentioned in Medication Guides. Do not use ABSORICA for a condition for which it was not prescribed. Do not give ABSORICA to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about ABSORICA. If you would like more information, talk with your doctor.

You can ask your doctor or pharmacist for information about ABSORICA that is written for health care professionals. You can also call iPLEDGE program at 1-866-495-0654 or visit www.ipledgeprogram.com.

What are the ingredients in ABSORICA?

Active ingredient: Isotretinoin, USP

Inactive ingredients: Propyl gallate, sorbitan monooleate, soybean oil and stearoyl polyoxylglycerides. Gelatin capsules contain the following dye systems: 10 mg – iron oxide (yellow), potassium hydroxide, propylene glycol, shellac and titanium dioxide; 20 mg – iron oxide (red), potassium hydroxide, propylene glycol, shellac and titanium dioxide; 25 mg – FD&C Blue #1, FD&C Yellow #5, FD&C Yellow #6, povidone, propylene glycol, shellac, sodium hydroxide and titanium dioxide; 30 mg – iron oxide (black, red and yellow), potassium hydroxide, povidone, propylene glycol, shellac, sodium hydroxide and titanium dioxide; 35 mg – FD&C Blue #2, iron oxide (black, red and yellow), povidone, propylene glycol, shellac, sodium hydroxide and titanium dioxide; and 40 mg – iron oxide (black, red and yellow), potassium hydroxide, povidone, propylene glycol, shellac, sodium hydroxide and titanium dioxide.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Dilantin is a registered trademark of Warner-Lambert Company LLC.

Distributed By:

Ranbaxy Laboratories Inc.

Ranbaxy Laboratories Inc. Jacksonville, FL 32257 USA

GK-244 Revised: xx 2014

Package/Label Display Panel

Attention Pharmacist: Dispense with enclosed Medication Guide.

NDC 10631-115-69

Absorica® (isotretinoin) Capsules

10 mg

Each capsule contains 10 mg Isotretinoin, USP

10 Capsules

Prescription Pack

PATIENT: READ INFORMATION CAREFULLY

Rx only



Absorica Causes Serious Birth Defects

Highlights of Warning to Female Patients.

(It is important to watch the DVD and read all information in the materials given to you by your doctor.)

- ▲ You MUST NOT take Absorice if you are pregnant because any amount can cause severe birth defects, even if taken for short periods during pregnancy.
 ▲ You MUST NOT become pregnant 1 month before, during, and for 1 month after you stop taking
- Absorica.

 A You will not get your first prescription for Absorica until there is proof you have had 2 negative pregnancy tests as instructed by your doctor (a negative test means that it does not show pregnancy) and you have interacted with the iPLEDGE system to answer questions about program sequinoments.

 A You cannot get monthly refills for Absorica unless there is proof that you have had a negative pregnancy test conducted in a lab every month during Absorica treatment.

 Even the best methods of birth control can fail. Therefore, 2 separate, effective forms of birth control
- must be used at the same time for at least 1 month before, during, and for 1 month after you stop
- ▲ Stop taking Absorice right away and cell your doctor immediately if you have sex without birth control miss your period or think you are pregnant while you are taking Absorica. If you think you are pregnant in the month after you have stopped Absorica treatment, call your doctor immediately.

Manufacturad for: A.Cheelaceecond BPC. Jacks unville, FL 32257 USA





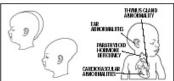


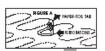
91 mm

FEMALE PATIENTS: DO NOT GET PREGNANT

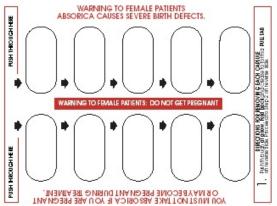
Very severe birth defects have occurred with isotretinoin use including:

- Severe Internal Defects: defects that you cannot see—involving the brain (including lower IQ scores), heart, glands and nervous system.
- Severe External Defects: defects that you can see—such as low-set, deformed or absent ears, wide-set eyes, depressed bridge of nose, enlarged head and small chin.





STORE AT 20° C - 25° C (68° F - 77° F), EXCURSION PERMITTED BETWEEN 15° C - 30° C (59° F - 86° F) [SEE USP C ONTROLLED ROOM TEMPERATURE]. PROTECT FROM LIGHT.



YOU MUST NOT TAKE ABSORICA IF YOU ARE PREGNANT

IMPORTANT INFORMATION FOR ALL PATIENTS:

It is important for your health that you read all the information you received with this prescription and from your doctor.

This package provides **reminders** of important safety facts about Absorica, but it does **not** contain all the information you need to know. It is important for you to know how to take Absorica correctly and what side effects to watch for.

Read all the information you get about Absorba from your doctor and pharmacist, including the Medication Guide provided with this package.

You should read, understand and sign a <u>Patent Information/Informed Consentform</u> before you take Absorba. Contact your doctor if you have not signed this form (male patients and female patients who cannot get pregnant must sign 1 form and female patients who can get pregnant must sign 2 forms).

Never share Absortion because it can cause serious side effects including severe birth defects.

- Before you start taking Absorba, tell your doctor if you:

 Are currently taking an oral or injected confacuteroid or an anticonvulsant
 (seizure) medication.

 Take part in sports where you are more likely to break a bone.
- Have mental problems, anorexia nervosa (a type of eating disorder), back pain, a history of problems with healing of bone fractures, or problems with bone metabolism.



Special Warning for Female Patients

CAUSES BIRTH DEFECTS



Absoriac causes serious bith defects. Do NOT take Absoriac if you are pregnant.
It is very important for you to read and understand the information about preventing pregnancy lound in this package, the Medication Guide, and the motorials given to you by your dooler. It is very important for you be interact with the PLEDGE system to arever questions about program requirements and view the DVD at your obotods's office.
If you do not have the Medication Guide, and the patient booklets about pregnancy prevention, don't start taking Absoriac. Call your doolor.

Most people have further questions after reading so much important information about pregnancy prevention and birth defects. If there is anything you are not sure about, do not take Absociac unit your questions have been answered by your doctor. Mental problems and suicide

Mental problems and suicids Some patients have become depressed or developed other serious mental problems while they were taking isotretinoin or shortly after stopping isotretinoin. Some patients taking isotretinoin have had throughts of ending their own lives (suicidal throughts). Some people have tried to end their own lives (afterapted suicide) and some people have ended their own lives (committed suicide). There have been reports of patients on isotretinoin becoming aggressive or violent. No are knows is joint-tertinoin outset these problems or behaviors or if they would have happened even if the person did not take isotretinoin.

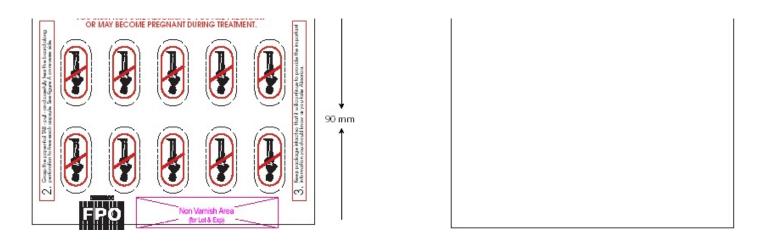
Stop taking Absorica and call your doctor right away if you or a family member notices that you have any of the following signs and symptoms of depression or psychosis:



- Start to feel said or have crying spells.
 Lase interest in activities you once enjoyed.
 Sleep too much or have trouble sleeping.

Become more irritable, angry, or aggressive than usual (for example, temper authorsts, thoughts of violences).
Have a change in your appetite or body weight.
Have houble concentrating.
Within any than from you frend as family.
Within any than you frend as family.
Within any than you frend as family.
Within any than you frend as family.
Have feelings of worthlessness or guit.
Start having thoughts about hutting yourself or taking your own life (suicidal thought).
Start acting an dangerous impulses.
Start acting an dangerous impulses.
Start acting on dangerous impulses.
Start acting on dangerous involves.
Start acting on the start of the start acting on the problems or if you be actively medicines or if you have not make the start of the start acting on the problems on this list or any other unusual or severe problems. If not treated, they could lead to serious health problems, Serious permanent problems do not happen often.
Headaches, noused, varniting, bursed vision (increased brain pressure).
Severe stomach pain, diamteria, rectableseding, or touble swallowing.
Velaving of your skin or eyes and/or dark urine.
Changes in heating.
Alergia reactions (if you know you are sersitive to "parabers", tell your doctor because if a presservative in the gelatin capsule of Absorica).
Bare or muside pain.
Vision changes, including trouble seeing at right (this can start suddenly, so be very careful when driving or operating any vehicle at right).
Persister theres, chile, or sers trout.
Persister theres, chile, or sers trout.
Common side effects that are not serious but that you should tell your doctor about.
How to take Absorica.





Package/Label Display Panel

NDC 10631-115-31

Absorica® (isotretinoin) Capsules

10 mg

Each capsule contains 10 mg Isotretinoin, USP

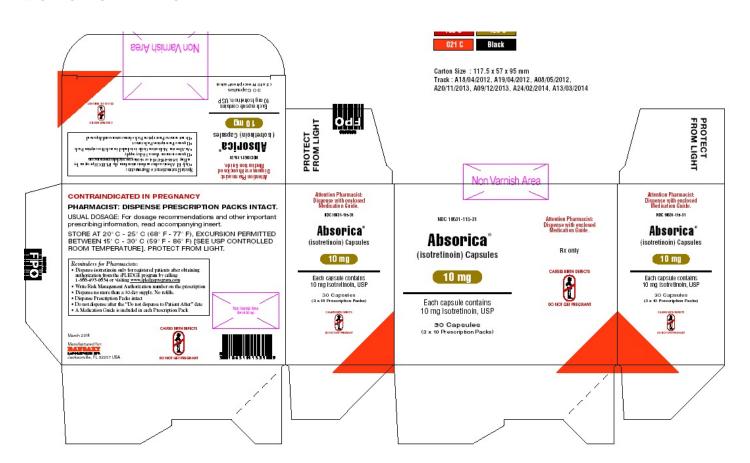
30 Capsules (3 x 10 Prescription Packs)

Attention Pharmacist: Dispense with enclosed Medication Guide.

Rx only

CAUSES BIRTH DEFECTS

DO NOT GET PREGNANT



Package/Label Display Panel

Attention Pharmacist: Dispense with enclosed Medication Guide.

NDC 10631-116-69

Absorica® (isotretinoin) Capsules

20 mg

Each capsule contains 20 mg Isotretinoin, USP

10 Capsules

Prescription Pack

PATIENT: READ INFORMATION CAREFULLY

Rx only



FEMALE PATIENTS: DO NOT GET PREGNANT

Absorica Causes Serious Birth Defects

Highlights of Warning to Female Patients.

(It is important to watch the DVD and read all information in the materials given to you by your doctor.)

- ▲ You MUST NOT take Absorica if you are pregnant because any amount can cause severe birth
- defects, even if taken for short periods during pregnancy.

 A You MUST NOT become pregnant 1 month before, during, and for 1 month after you stop taking
- ▲ You will not get your first prescription for Absorba until there is proof you have had 2 negative ■ In an integration and interpretation of the control of the c
- pregnancy test conducted in a lab every month during Absorbca treatment.

 Even the best methods of birth control can fail. Therefore, 2 separate, effective forms of birth control must be used at the same time for at least 1 month before, during, and for 1 month after you stop taking Absoriga.
- Asking Absorice right away and call your doctor immediately if you have see without birth control, miss your period or think you are prognant while you are taking Absorice. If you think you are prognant in the morth after you have stopped Absorice treatment, call your doctor immediately.





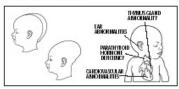
March 2014



FEMALE PATIENTS: DO NOT GET PREGNANT

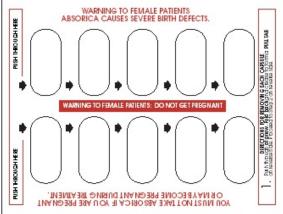
Very severe birth defects have occurred with isotretinoin use including:

- Severe Internal Defects: defects that you cannot see—involving the brain (including lower IQ scores), heart, glands and nervous system.
- Severe External Defects: defects that you can see—such as low-set, deformed or absent ears, wide-set eyes, depressed bridge of nose, enlarged head and small chin.





STORE AT 20° C - 25° C (68° F - 77° F), EXCURSION PERMITTED BETWEEN 15° C - 30° C (59° F - 86° F) (SEE USP CONTROLLED ROOM TEMPERATURE). PROTECT FROM LIGHT.



IMPORTANT INFORMATION FOR ALL PATIENTS:

It is important for your health that you read all the information you received with this prescription and from your doctor.

This package provides **reminders** of important safety facts about Absorica, but it does **not** contain all the information you need to know. It is important for you to know how to take Absorica correctly and what side effects to watch for.

Read all the information you get about Absorba from your doctor and pharmacist, including the Medicalion Guide provided with this package.

You should read, understand and sign a <u>Patient Information/Informed Consentiorm</u> before you take Absorba. Contact your deator if you have not signed this form (male patients and female patients who cannot get pregnant must sign 1 form and female patients who can get pregnant must sign 2 forms).

Never share Absorioa because it can cause serious side effects including severe birth defects

- Before you start taking Absorice, tell your doctor if you:

 Are outrently taking an oral or injected conficusteroid or an anticonvulsant (setsure) medication.

 Take part in sports where you are more likely to break a bone.
- Have mental problems, an arexia nervosa (a type of eating disorder), back pain, a history of problems with healing of bone fractures, or problems with bone metabolism.



91 mm

91 mm

Special Warning for Female Patients

CAUSES BIRTH DEFECTS



DO NOT GET PREGNANT

Absorica causes serious birth defects. Do NOT take Absorica if you are pregnant.

if you are pregnant.

It is very important for you to sead and understand the information about preventing pregnancy found in this package, the Medication Galde, and the motionist given to you by your dooter. It is very important for you to interact with the PLEDGE system to arever questions about program requirements and view the DVD of your obotics's office.

If you do not have the Medication Guide, and the patient booklets about pregnancy prevention, don't start taking Absorica. Call your dooter.

Most people have further questions after reading so much important information about pregnancy prevention and bith defeats. If here is anything you are not sue about, do not take Absorba until your questions have been answered by your dector. Mental problems and suicide

Martial problems and suisids. Some patients have become depressed or developed other serious mental problems while they were taking isotretinoin or shortly after stopping isotretinoin. Some patients taking isotretinoin have had thoughts of ending their own lives (quididal thoughts). Some people have tried to end their own lives (afterproted suidide) as some people have ended their own lives (committed suicide). There have been reports of patients on isotretinoin becomin aggressive or violent. No and knows it isotretinoin caused these problems or behaviors or if they would have happened even if the person did not take isotretinoin.

Stop taking Absorica and call your doctor right away if you or a family member notices that you have any of the following signs and symptoms of depression or psychosis:



- Start to feel said or have crying spells.
 Lose interest in activities you once enjoyed.
 Sleep too much or have trouble sleeping.
- Become more initiable, angry, or aggressive than usual (for example, temper outbursts, thoughts of violence).

- cutbusts, thoughts of violence).

 Have a charge in your appetite or body weight.

 Have houble concentrating.

 Withdraw from your finends or family.

 Feel Ree you have no energy.

 Have feelings of worthlesenses or guit.

 Shart having thoughts about hutting youself or taking your own life (suicidal houghts).

 Shart having thoughts about hutting youself or taking your own life (suicidal houghts).

 Shart seeing or hogarise simpulses.

 Shart seeing or hogarise manual for the shart seeing or hogarise more one in your family has ever had a mental lifness or if you take any medicines for a mental lifness (for example, depression).

you take any medicines for a mental lithess (for example, depression).

Other serious side effects to watch for Stop taking absorbed and select to watch for Stop taking absorbed and call your declor if you develop any of the problems on this list or any other unusual or severe problems. If not theated, they could lead to serious health problems, Serious permanent problems do not happen often.

Headaches, nousea, varniting, blured vision (increased brain pressure).

Severe stomach pain, dianthea, restal televating, or trouble swallowing.

Yellowing of your skin or eyes and/or dark urine.

Changes in heating.

Allergic reactions (if you know you are sensitive to "parabere", tell your doctor because it is a preservative in the gelatin capsule of Absorba.

Brane or muscle pain.

Vision changes, holding thouble seeing at night (this can start suddenly, so be very careful when driving or operating any vehicle at night).

Persistent fever, chils, or sore throat.

Other Important Information is found in the Medication Guide and in the booklets

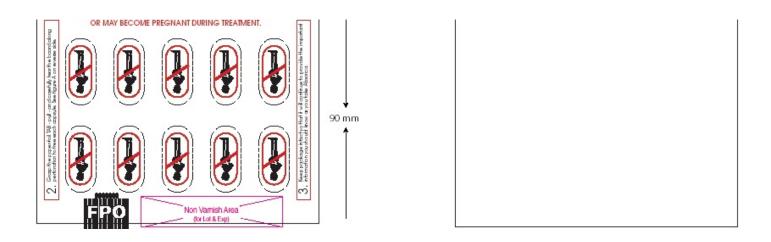
- Presisters rever, or case, of sore triods.
 Other Important Information is found in the Medication Guide and in the booklets from your doctor.
 Common aide effects that are not serious but that you should tell your doctor about.

- How to take Absorioa.
 Things to avoid during Absorioa treatment.
 Ways to get more information if you need it.



91 mm





NDC 10631-116-31

Absorica® (isotretinoin) Capsules

20 mg

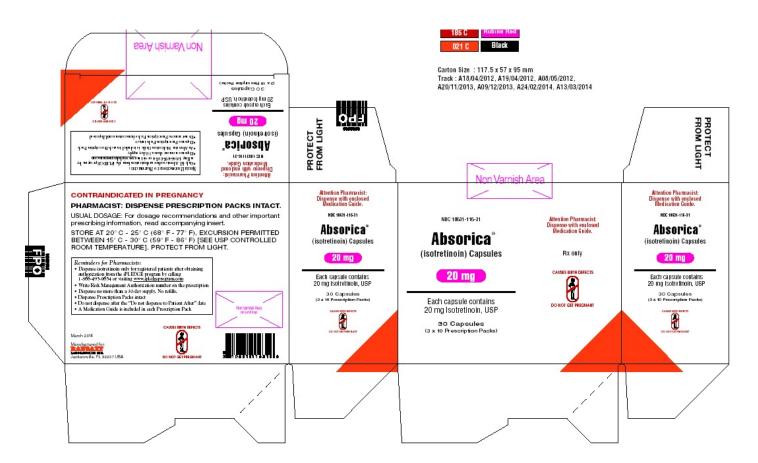
Each capsule contains 20 mg Isotretinoin, USP

30 Capsules (3 x 10 Prescription Packs)

Attention Pharmacist: Dispense with enclosed Medication Guide.

Rx only

CAUSES BIRTH DEFECTS



Attention Pharmacist: Dispense with enclosed Medication Guide.

NDC 10631-133-69

Absorica® (isotretinoin) Capsules

25 mg

Each capsule contains 25 mg Isotretinoin, USP

10 Capsules

Prescription Pack

PATIENT: READ INFORMATION CAREFULLY



FEMALE PATIENTS: DO NOT GET PREGNANT

Absorica Causes Serious Birth Defects

Highlights of Warning to Female Patients.

(It is important to watch the DVD and read all information in the materials given to you by your doctor.)

- ▲ You MUST NOT take Absorica if you are pregnant because any amount can cause severe birth
- defects, even if taken for short periods during prognancy.

 A You MUST NOT become pregnant 1 month before, during, and for 1 month after you stop taking
- ▲ You will not get your first prescription for Absorice until there is proof you have had 2 negative pregnancy tests as instructed by your doctor (a negative test means that it does not show prognancy) and you have interacted with the iPLEDGE system to answer questions about program requirements.

 A You cannot get monthly refile for Absorba unless there is proof that you have had a negative
- pregnancy lest conducted in a lab every month during Absonica treatment.

 A Even the best methods of birth control can fail. Therefore, 2 separate, effective forms of birth control must be used at the same time for at least 1 month before, during, and for 1 month after you stop taking Absorica.
- A Stop taking Alborica right away and call your dootor immediately if you have sex without birth control, miss your period or think you are prognant while you are taking Absorice. If you think you are pregnant in the morth after you have stopped Absorice treatment, call your dootor immediately.





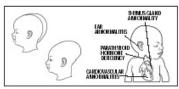
March 2014

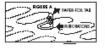


FEMALE PATIENTS: DO NOT GET PREGNANT

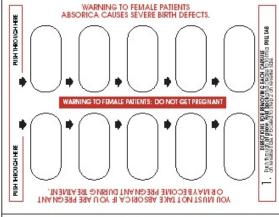
Very severe birth defects have occurred with isotretinoin use including:

- Severe Internal Defects: defects that you cannot see—involving the brain (including lower IQ scores), heart, glands and nervous system.
- Severe External Defects: defects that you can see—such as low-set, deformed or absent ears, wide-set eyes, depressed bridge of nose, enlarged head and small chin.





STORE AT 20° C - 25° C (68° F - 77° F), EXCURSION PERMITTED BETWEEN 15° C - 30° C (59° F - 86° F) (SEE USP CONTROLLED ROOM TEMPERATURE). PROTECT FROM LIGHT.



YOU MUST NOT TAKE ABSORICA IF YOU ARE PREGNANT

IMPORTANT INFORMATION FOR ALL PATIENTS:

It is important for your health that you read all the information you received with this prescription and from your doctor.

This package provides reminders of important safety facts about Absorica, but it does not contain all the information you need to know. It is important for you to know how to take Absorica correctly and what side effects to watch for.

Read all the information you get about Absorba from your doctor and pharmacist, including the Medication Guide provided with this package.

You should read, understand and sign a Patent Information/Informed Consentform before you take Absorba. Contact your deator if you have not signed this form (male patients who cannot get pregnant must sign 1 form and female patients who can get pregnant must sign 2 forms).

Never share Absorica because it can cause serious side effects including severe birth defects.

- Before you start taking Absorice, tell your declar if you:

 Are autentity taking an area or injected conficateroid or an anticonvulsant (seizure) medication.

 Take part in sports where you are more likely to break a bone.

 Take part in sports where you are more likely to break a bone.

 Have mental problems, and exica nervosa (a type of eating disorder), back pain, a history of problems with healing of bone fractures, or problems with bone metabolism.



91 mm

91 mm

Special Warning for Female Patients

CAUSES BIRTH DEFECTS



DO NOT GET PREGNANT

Absorica causes serious birth defects. Do NOT lake Absorica if you are pregnant.

if you are pregnant.
It is very important for you to sead and understand the internation about preventing pregnancy found in this package, the Medication Guide, and the malarists given to you by your dooter. It is very important for you to interact with the PLEDGE system to arever questions about program requirements and view the DVD of your dooter's office.
If you do not have the Medication Guide, and the patient booklets about pregnancy prevention, don't start taking Absorica. Call your dooter.

Most people have further questions after reading so much important information about pregnancy prevention and birth defects. If there is anything you are not sure about, do not have absorbed until your questions have been answered by your doctor.

do not take Absonce unit your questions have been answered by your doctor. Manfal problems and suicise some depressed or developed other serious mental problems while they were taking isotretinoin or shortly after stopping isotretinoin. Some patients taking isotretinoin have had thoughts of ending their own lives (suicidal thoughts). Some people have tried to end their own lives (attempted suicide) and some people have ended their own lives (committed suicide). These have been reports of patients on isotretinoin becoming aggressive or violent. No one knows if solvetinoin acused these problems or behaviors or if they would have happened even if the person did not take isotretinoin.

Stop taking Absorica and call your doctor right away if you or a family member notices that you have any of the following signs and symptoms of depression or psychosis:



- Start to feel said or have crying spells.
 Lose interest in activities you once enjoyed.
 Sleep too much or have trouble sleeping.

- Become more iritiable, angry, or aggressive than usual (for example, temper authority, thoughts of violence).
 Have a charge in your appetite or body weight.
 Have houble concentrating.
 Withdraw from your friends or family.
 Feel Rie you have no energy.
 Have feelings of worthleanness or guilt.
 Start having thoughts about hutting yourself or taking your own life (suicidal thought).
 Start baving on dangerous impulses.
 Start seeing on loaning things that are not real.
 Ell your doot if you or someone in your family has ever had a mental litness or if youtske any medicines for a mental litness (for example, depression).
 Other serious side affects to watch for

- you take any medicines for a mental lithress (for example, depression).

 Other serious side effects to watch for Stop taking Absonice and call your doctor if you develop any of the problems on this list or any other unusual or severe problems. If not theated, they could lead to serious health problems, Serious permanent problems do not happen often.

 Headaches, nausea, vanniting, bluried vision (increased brain pressure).

 Severe stomach pain, dianthea, restal televating, or trouble swallowing.

 Veloving of your skin or eyes and/or dark urine.

 Changes in hearing.

 Allergic reactions (if you know you are sensitive to "parabene", tell your doctor because it is a preservative in the gelatin capsule of Absonica).

 Brane or muscle pain.

 Vision changes, including trouble seeing at night (this can start suddenly, so be very careful when driving or operating any vehicle at night).

 Presistent fever, chils, or sore throat.

 Other Importal Information is found in the Medication Guide and in the booklets

- Persitent fever, chils, or sore throat.

 Other Important Indemnation is found in the Madication Guide and in the booklets from your declor.

 Common side effects that are not serious but that you should tell your doctor about.

 How to take Absorica.

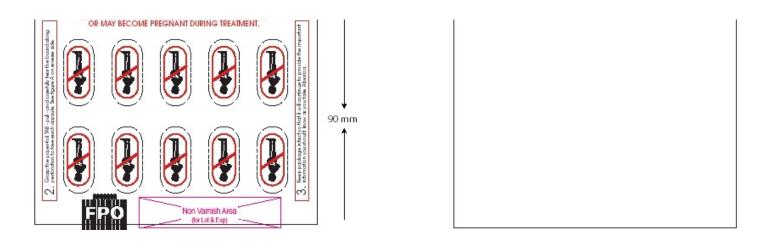
 Things to avoid during Absorica treatment.

 Ways to get more information if you need it.





91 mm



NDC 10631-133-31

Absorica® (isotretinoin) Capsules

25 mg

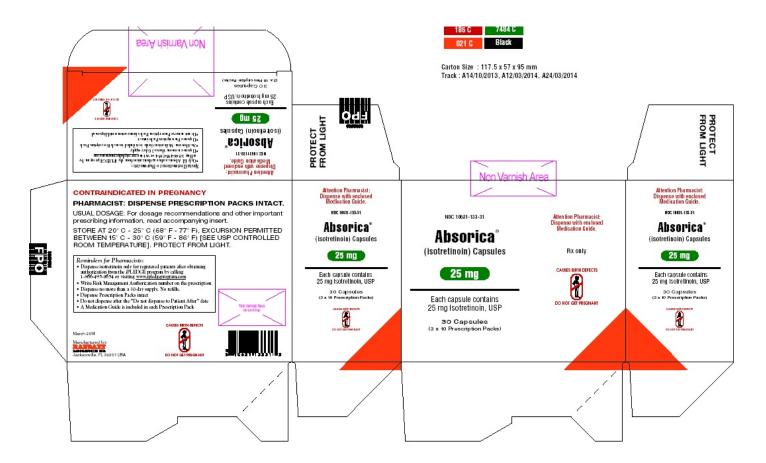
Each capsule contains 25 mg Isotretinoin, USP

30 Capsules (3 x 10 Prescription Packs)

Attention Pharmacist: Dispense with enclosed Medication Guide.

Rx only

CAUSES BIRTH DEFECTS



Attention Pharmacist: Dispense with enclosed Medication Guide.

NDC 10631-117-69

Absorica® (isotretinoin) Capsules

30 mg

Each capsule contains 30 mg Isotretinoin, USP

10 Capsules

Prescription Pack

PATIENT: READ INFORMATION CAREFULLY



Absorica Causes Serious Birth Defects

Highlights of Warning to Female Patients.

(It is important to watch the DVD and read all information in the materials given to you by your doctor.)

- ▲ You MUST NOT take Absorica if you are pregnant because any amount can cause severe birth
- defects, even if taken for short periods during programory.

 A You MUST NOT become program 1 month before, during, and for 1 month after you stop taking
- ▲ You will not get your first prescription for Absorica until there is proof you have had 2 negative programory tests as instructed by your doctor (a negative test means that it does not show programory) and you have interacted with the iPLEDGE system to answer questions about program requirements.
- ▲ You cannot get monthly refills for Absorica unless there is proof that you have had a negative
- pregnancy test conducted in a lab every month during Absorica treatment.

 A Even the best methods of birth control can fail. Therefore, 2 separate, effective forms of birth control must be used at the same time for at least 1 month before, during, and for 1 month after you stop
- taking Absonica.

 A Stop taking Absonica right away and call your doctor immediately if you have sex without birth control miss your period or think you are pregnant while you are taking Absorica. If you think you are pregnant in the month after you have stopped Absorica treatment, call your doctor immediately.

Manufactured for



March 2014



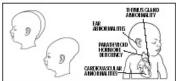
91 mm

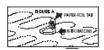
91 mm

FEMALE PATIENTS: DO NOT GET PREGNANT

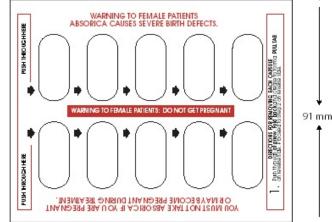
Very severe birth defects have occurred with isotretinoin use including:

- Severe Internal Defects: defects that you cannot see—involving the brain (including lower IQ scores), heart, glands and nervous system.
- Severe External Defects: defects that you can see—such as low-set, deformed or absent ears, wide-set eyes, depressed bridge of nose, enlarged head and small chin.





STORE AT 20° C - 25° C (68° F - 77° F), EXCURSION | PERMITTED BETWEEN 15° C - 30° C (59° F - 86° F) |SEE USP CONTROLLED ROOM TEMPERATURE|. | PROTECT FROM LIGHT.



YOU MUST NOT TAKE ABSORICA IF YOU ARE PREGNANT

IMPORTANT INFORMATION FOR ALL PATIENTS:

It is important for your health that you read all the information you received with this prescription and from your doctor.

This package provides reminders of important safety facts about Absorica, but it does not contain all the information you need to know. It is important for you to know how to take Absorica correctly and what side effects to watch for.

Read all the information you get about Absorioa from your doctor and pharmacist, including the Medication Guide provided with this package.

You should read, understand and sign a Patient Information/Informed Consentform before you take Absorica. Contact your doctor if you have not signed this form (male patients and fermale patients who connot pelp pregnant must sign 1 form and female patients who can get pregnant must sign 2 forms).

Never share Absortion because it can cause serious side effects including severe birth defects.

- Before you start taking Absorica, tell your doctor if you:

 Are currently taking an oral or injected confloasteroid or an anticonvulsant
 (seizure) medication.

 Take part in sports where you are more likely to break a bone.
- Have mental problems, anorexia nervosa (a type of eating disorder), back pain, a history of problems with healing of bone fractures, or problems with bone metabolism.



Special Warning for Female Patients

CAUSES BIRTH DEFECTS



DO NOT GET PREGNANT

Absorice causes serious birth defects. Do NOT take Absorice if you are pregnant.
It is very important for you to read and understand the intermatine about preventing pregnancy found in this package, the Medication Guide, and the moterable given to you by your doctor. It is very important for you to interact with the PLEDGE system to arever questions about program requirements and view the DVD of your doctor's office.
If you do not have the Medication Guide, and the patient booklets about pregnancy prevention, don't start taking Absorice. Call your doctor.

Most people have further questions after reading so much important information about pregnancy prevention and birth defects. If there is anything you are not sure about, do not take Absocial until your questions have been answered by your doctor.

Metal residence and picture.

Mental problems and suicide Some patients have become depressed or developed other serious mental problems while they were taking isohetinon or shortly after stopping isohetinon. Some patients taking isohetinon have had thoughts of ending their own lives (suicidal thoughts). Some people have tried to end their own lives (attempted suicide) and some people have ended their own lives (committed suicide). These have been reports of patients on isotretinon becoming aggressive or violent. No one knows is folder their inclusived these problems or behaviors or if they would have happened even if the person did not take isotretinon.

Stop taking Absorica and call your doctor right away if you or a family member notices that you have any of the following signs and symptoms of depression or psychosis:



- Start to feel sad or have arying spells.
 Lose interest in activities you once enjoye.
 Sleep too much or have trouble sleeping.

- Sleep too much or have trouble sleeping.

 Become more irritable, angry, or aggressive than usual (for example, temper authorsts, thoughts of violence).
 Have a charge in your appetite or body weight.

 Have a charge in your appetite or body weight.

 Have the table conceptioning traity.

 Feel Rey you have no energy.

 Have feelings of worth leaness or guitt.

 Start braining thoughts about hurting yourself or taking your own life (suicidal thoughts).

 Start acting on dangerous imputes.

 Start acting on dangerous imputes.

 Start acting or hearing things that are not real.

 Tell your doctor if you or someone in your family has ever had a mental illness or if your toke any medicines for a mental littless (for example, depression).

 Other serious side affects to watch the Sop but reg the problems on this list or any other unusual or severe problems. If not treated, they could lead to serious health problems, serious permanent problems do not happen often.

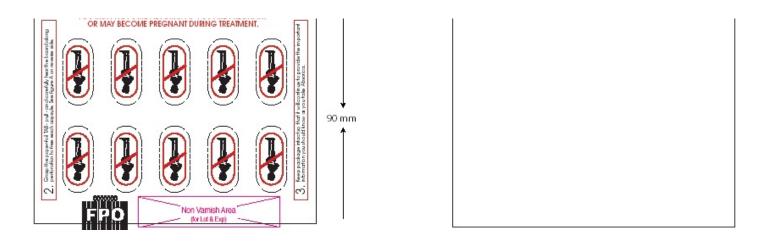
 Feel Rey work in a reyes and/or dark urine.

 Allengic reactions (if you know you are sensitive to "parabere", tell your doctor because it is a preservative in the gelatin capsule of Absorica).

 Brone or muscle pain.

 Vision changes, including trouble seeing at right (this can start suddenly, so be very careful when diving or operating any vehicle at night).

 Other proportial Information is found in the Medication Guide and in the booklets force your declars.
- Persistent fever, chils, or sore throat.
 Other Important Information is found in the Medication Guide and in the book lefs from your doctor.
 Common side effects that are not serious but that you should tell your doctor about.
 How to take Absociaca.
 Things to avoid during Absociaca treatment.
 Ways to get more information if you need it.



NDC 10631-117-31

Absorica® (isotretinoin) Capsules

30 mg

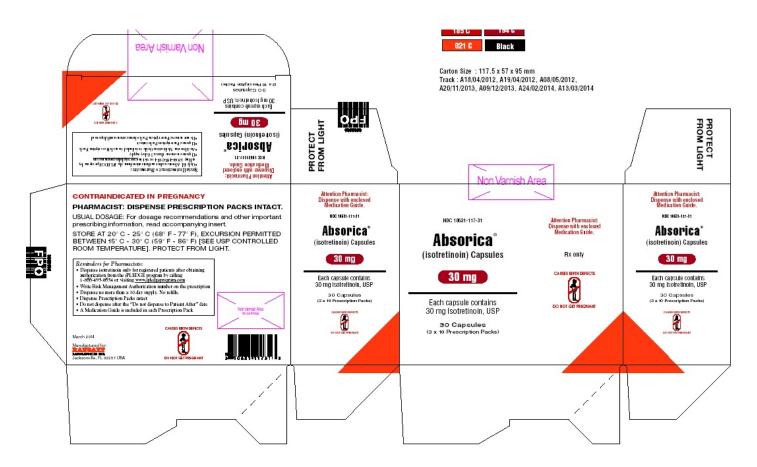
Each capsule contains 30 mg Isotretinoin, USP

30 Capsules (3 x 10 Prescription Packs)

Attention Pharmacist: Dispense with enclosed Medication Guide.

Rx only

CAUSES BIRTH DEFECTS



Attention Pharmacist: Dispense with enclosed Medication Guide.

NDC 10631-134-69

Absorica® (isotretinoin) Capsules

35 mg

Each capsule contains 35 mg Isotretinoin, USP

10 Capsules

Prescription Pack

PATIENT: READ INFORMATION CAREFULLY



KX OUT Y

READINFO RMATION CAREFULLY PATIENT

10 Capsules Prescription Pack

35 mg Isotrefinoin, USP Esch capsule contains



(is ofretinoin) Capsules

Sorica

69-#£1-1£901-DON

Medication Guide. Attention Pharmacist: Descione Aftweensed



FEMALE PATIENTS: DO NOT GET PREGNANT

Absorica Causes Serious Birth Defects Highlights of Warning to Female Patients.

(It is important to watch the DVD and read all information in the materials given to you by your doctor.)

- ▲ You MUST NOT take Absorica if you are pregnant because any amount can cause severe birth defects, even if taken for short periods during pregnancy.
 ▲ You MUST NOT become pregnant 1 month before, during, and for 1 month after you stop taking
- A You will not get your first prescription for Absorica until there is proof you have had 2 negative pregnancy tests as instructed by your doctor (a negative test means that it does not show pregnancy) and you have interacted with the iPLEDGE system to answer questions about program requirements.
- ▲ You cannot get monthly refills for Absorica unless there is proof that you have had a negat pregnancy test conducted in a lab every month during Absorica treatment.

 A Even the best methods of birth control can fail. Therefore, 2 separate, effective forms of birth
- control must be used at the same time for at least 1 month before, during, and for 1 month after you stop taking Absorica.
- Stop taking Absorica right away and call your doctor immediately if you have sex without birth control, miss your period or think you are pregnant while you are taking Absorica. If you think you are pregnant in the month after you have stopped Absorica treatment, call your doctor immediately.





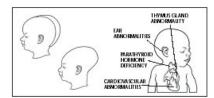
July 2014

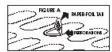


FEMALE PATIENTS: DO NOT GET PREGNANT

Very severe birth defects have occurred with isotretinoin use including:

- Severe Internal Defects: defects that you cannot see—involving the brain (including lower IQ scores), heart, glands and nervous system.
- Severe External Defects: defects that you can see—such as low-set, deformed or absent ears, wide-set eyes, depressed bridge of nose, enlarged head and small chin.





STORE AT 20° C - 25° C (68° F - 77° F), EXCURSION PERMITTED BETWEEN 15° C - 30° C (59° F - 86° F) [SEE USP CONTROLLED ROOM TEMPERATURE].
PROTECT FROM LIGHT.

IMPORTANT INFORMATION FOR ALL PATIENTS:

It is important for your health that you read all the information you received with this prescription and from your doctor.

This package provides reminders of important safety facts about Absorica, but it does not contain all the information you need to know. It is important for yo to know how to take Absorica correctly and what side effects to watch for.

Read all the information you get about Absorica from your doctor and pharmacist, including the Medication Guide provided with this package.

You should read, understand and sign a Patient Information/Informed Consent form before you take Absorica. Contact your doctor if you have not signed this form (male patients and female patients who cannot get pregnant must sign 1 form and female patients who can get pregnant must sign 2 forms).

> Never share Absorica because it can cause serious side effects including severe birth defects

Before you start taking Absorica, tell your doctor if you:

- Are currently taking an oral or injected conficosteroid or an anticonvulsant (seizure) medication.
 Iake part in sports where you are more likely to break a bone.
- Have mental problems, anorexia nervosa (a type of eating disorder), back pain, a history of problems with healing of bone fractures, or problems with bone metabolism.

Special Warning for Female Patients

CAUSES BIRTH DEFECTS



DO NOT GET PREGNANT

Absorica causes serious birth defects. Do NOT take Absorica if you are pregnant.

It is very important for you to read and understand the information about preventing pregnancy found in this package, the Medication Guide, and the materials given to you by your doctor. It is very important for you to interact with the iPLEDGE system to answer questions about program requirements and view the DVD at your doctor's office. If you do not have the Medication Guide, and the patient booklets about pregnancy prevention, don't start taking Absorica. Call your doctor.

Most people have further questions after reading so much important information about pregnancy prevention and birth defects. If there is anything you are not sure about, do not take Absorica until your questions have been answered by your doctor. Mental problems and suicide

Some patients have become depressed or developed other serious mental problems while they were taking isotretricin or shortly after stopping isotretricin. Some patients taking isotretricin or shortly after stopping isotretricin. Some patients taking isotretinoin have had thoughts of ending their own lives (submitted unicide) and some people have ended their own lives (committed suicide). There have been reports of patients on isotretinoin becoming aggressive or violent. No one knows if isotretricin caused these problems or behaviors or if they would have happened even if the person aid

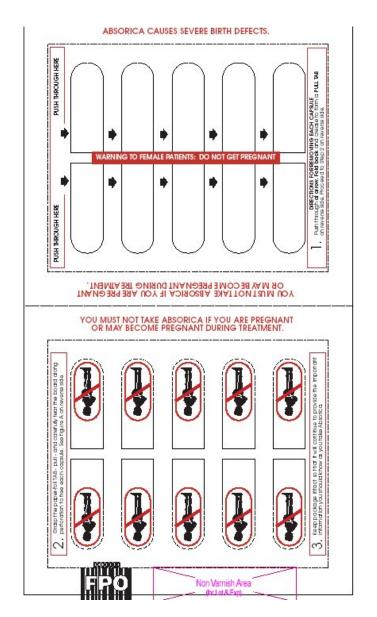
Stop taking Absorica and call your doctor right away if you or a family member notices that you have any of the following signs and symptoms of depression or psychosis:

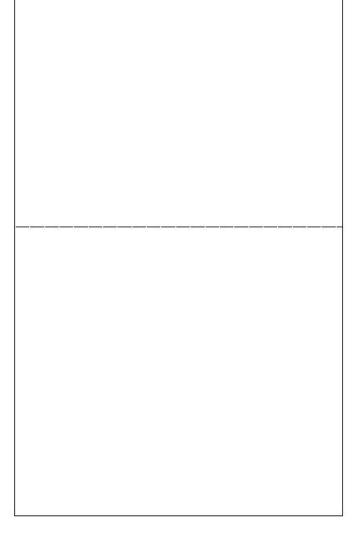
- · Start to feel sad or have crying spells.
- Lose interest in activities you once enjoyed.

Sleep too much or have trouble sleeping.
Become more inflable, angry, or aggressive than usual (for example, temper outbursts, thoughts of violence).
Have a change in your appetite or body weight.
Have touble concentrating.
Withdraw from your friends or family.
Feel like you have no energy.
Have feelings of worthlessness or guilt.
Start having thoughts about hurting yourself or taking your own life (suicidal thoughts).
Start having thoughts about hurting yourself or taking your own life (suicidal thoughts).
Start seeing or heating things that are not real.
Tell your doctor if you or someone in your family has ever had a mental ilness or if you take any medicines for a mental illness (for example, depression).
Other serious side effects to watch for Stop taking Absorica and call your doctor if you develop any of the problems on this list or any other unusual or severe problems. If not treated, they could lead to serious health problems. Serious permanent problems do not happen offen.
Headaches, nausea, vomitting, blured vision (increased brain pressure).
Severe stomach pain, diarrhea, rectal bleeding, or trouble swallowing.
Yellowing of your skin or eyes and/or dark urine.
Changes in hearing.
Allergic reactions (if you know you are sensitive to "parabens", tel your doctor because it is a preservative in the gelatin capsule of Absorica).

- Bone or muscle pain.
- Vision changes, including trouble seeing at right (this can start suddenly, so be very careful when driving or operating any vehicle at night).
 Persistent fever, chills, or sore throat.
 Other Important Information is found in the Medication Guide and in the booklets
- from your doctor:
- Common side effects that are not serious but that you should tell your doctor about.
 How to take Absorica.
- Things to avoid during Absorica treatment.
- Ways to get more information if you need it.

WARNING TO FEMALE PATIENTS





NDC 10631-134-31

Absorica® (isotretinoin) Capsules

35 mg

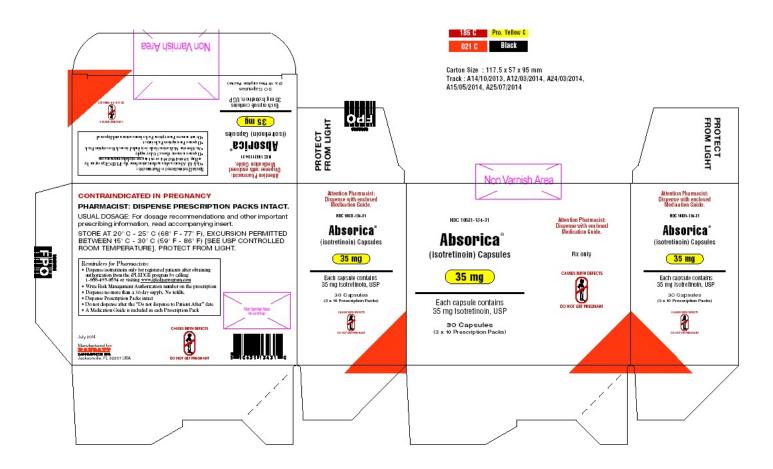
Each capsule contains 35 mg Isotretinoin, USP

30 Capsules (3 x 10 Prescription Packs)

Attention Pharmacist: Dispense with enclosed Medication Guide.

Rx only

CAUSES BIRTH DEFECTS



Attention Pharmacist: Dispense with enclosed Medication Guide.

NDC 10631-118-69

Absorica® (isotretinoin) Capsules

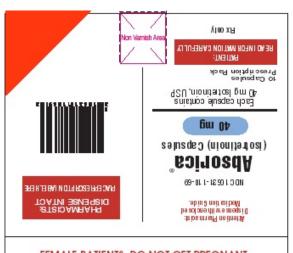
40 mg

Each capsule contains 40 mg Isotretinoin, USP

10 Capsules

Prescription Pack

PATIENT: READ INFORMATION CAREFULLY



FEMALE PATIENTS: DO NOT GET PREGNANT

Absorica Causes Serious Birth Defects

Highlights of Warning to Female Patients.

(It is important to watch the DVD and read all information in the materials given to you by your doctor.)

- ▲ You MUST NOT take Absorica if you are pregnant because any amount can cause severe birth
- defects, even if taken for short periods during pregnancy.

 A You MUST NOT become pregnant 1 month before, during, and for 1 month after you stop taking
- ▲ You will not get your first prescription for Absorica until there is proof you have had 2 negative
- pregnancy tests as instructed by your doctor (a negative test means that it does not show pregnancy) and you have interacted with the iPLEDGE system to answer questions about program requirements.

 You cannot get markly refills for Associa unless there is proof that you have had a negative pregnancy test conducted in a lab every month during Associa treatment.

 Even the best methods of birth control can fail. Therefore, 2 separate, effective forms of birth control
- must be used at the same time for at least 1 month before, during, and for 1 month after you stop taking Absorica.
- ▲ Stop taking Absorica right away and call your doctor immediately if you have sex without birth control miss your period or think you are pregnant while you are taking Absorba. If you think you are pregnant in the month after you have stopped Absorba treatment, call your doctor immediately.



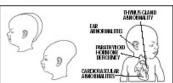


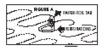


FEMALE PATIENTS: DO NOT GET PREGNANT

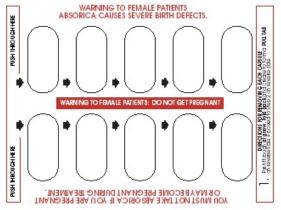
Very severe birth defects have occurred with isotretinoin use including:

- Severe Internal Defects: defects that you cannot see—involving the brain (including lower IQ scores), heart, glands and nervous system.
- Severe External Defects: defects that you can see—such as low-set, deformed or absent ears, wide-set eyes, depressed bridge of nose, enlarged head and small chin.





STORE AT 20° C - 25° C (68° F - 77° F), EXCURSION PERMITTED BETWEEN 15° C - 30° C (59° F - 86° F) (SEE USP CONTROLLED ROOM TEMPERATURE). PROTECT FROM LIGHT.



IMPORTANT INFORMATION FOR ALL PATIENTS:

It is important for your health that you read all the information you received with this prescription and from your doctor.

This package provides **reminders** of important safety facts about Absorica, but it does **not** contain all the information you need to know. It is important for you to know how to take Absorica correctly and what side effects to watch for.

Read all the information you get about Absorba from your doctor and pharmacist, including the Medication Guide provided with this package.

You should read, understand and sign a Patent Information/Informed Consentform before you take Absorica. Contact your dector if you have not signed this form (male patients and female patients who cannot get pregnant must sign 1 form and female patients who can get pregnant must sign 2 forms).

Never share Absorica because it can cause serious side effects including severe birth defects.

- Before you start taking Absorica, let your doctor if you:

 Are currently taking an aral or injected conficusteroid or an anticonvulsant
 (seizure) medication.

 Take part in sports where you are more likely to break a bone.
- Have mental problems, ancrexia nervosa (a type of eating disorder), back pain, a history of problems with healing of bone fractures, or problems with bone metabolism.



91 mm

91 mm

Special Warning for Female Patients

CAUSES BIRTH DEFECTS



DO NOT GET PREGNANT

Absorice causes serious birth defects. Do NOT take Absorice if you are pregnant.

It is very important for you to read and understand the information about preventing pregnancy found in this package, the Medication Guide, and the motorials given to you by your dooks. It is very important for you be interact with the PLEDGE system to arever questions about program requirements and view the DVD of your dooked's office.

If you do not have the Medication Guide, and the patient booklets about pregnancy prevention, don't start taking Absorice. Cell your doolor.

Most people have further questions after reading so much important information about pregnancy prevention and birth defects. If there is anything you are not sure about, do not take Absorica until your questions have been answered by your doctor.

Mental problems and suicide

Mental problems and suicide Some patients have become depressed or developed other serious mental problems while they were taking sichtetinori or shortly after stepping isotretinorin. Some patients taking isotretinorin have had thoughts of ending their own lives (suicidal thoughts). Some people have tried to end their own lives (afterprets suicide) and some people have ended their own lives (committed suicide). There have been reports of patients on isotretinorin becoming aggressive or violent. No one knows is lost efficient caused these problems or behaviors or if they would have happened even if the person did not take isotretinorin.

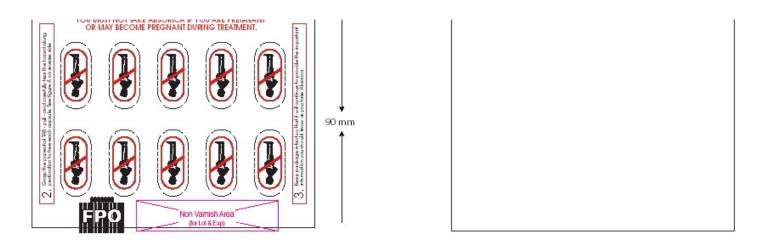
Stop taking Absorica and call your doctor right away if you or a family member notices that you have any of the following signs and symptoms of depression or psychosis:



- Start to feel sad or have arying spells.
- Lose interest in activities you once enjoye
 Sleep too much or have trouble sleeping.
- . Become more irritable, arigny, or aggressive than usual (for example, temper

- Become more irritable, angry, or aggressive than usual (for example, temper outbursts, thoughts of violence).
 Have a change in your appetite or body weight.
 Have that on the concentrating.
 Withind and that only one time of a change in your appetite.
 Have that the concentrating.
 Withind and that only one time of a change is the concentration of the concentration.
 Have feeling of worthlessness or guit.
 Start having thoughts about huiting youself or taking your own life (suicidal thoughts).
 Start seeing on dangerous impulses.
 Start seeing on hearing things that are not real.
 Tell your doctor if you dangerous impulses of the problems on this list or any offer unusual or severe problems. If not treated, they could lead to serious headth problems, Serious permanent problems do not happen often.
 Head of the poulse, noused, worthing, blured wise in (fracteased brain pressure).
 Head of the poulse, nouse, worthing, blured wise in (fracteased brain pressure).
 Velowing of your skin or eyes and/or dark wine.
 Changes in heading.
 Allerge reactions (fryou know you are sereitive to "parabeter", tell your doctor because it is a preservative in the gelatin capsule of Absorica).
 Bane or muscle pain.
 Vision changes, including trouble seeing at night (this can start suddenly, so be very careful when diving or operating any vehicle at night).
 Persistent fewer, chills, or sore throat.
- Other Important Information is found in the Medication Guide and in the booklets
- from your doctor:
 Common side effects that are not serious but that you should tell your doctor about.
- How to take Absorica.
 Things to avoid during Absorica treatment.
 Ways to get more information if you need it.

91 mm



NDC 10631-118-31

Absorica® (isotretinoin) Capsules

40 mg

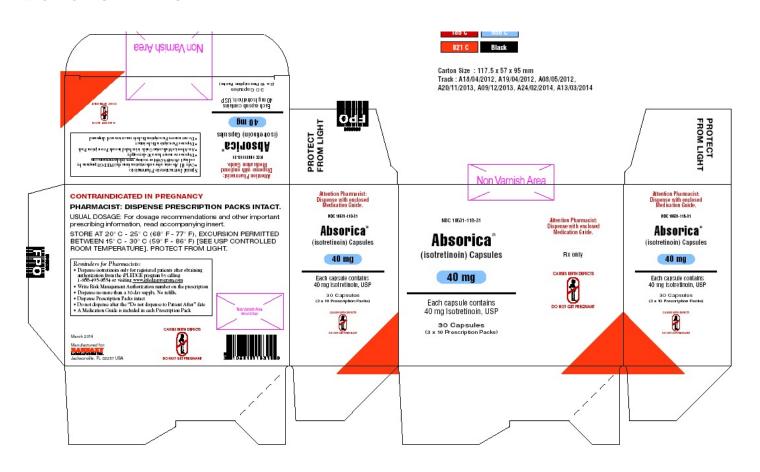
Each capsule contains 40 mg Isotretinoin, USP

30 Capsules (3 x 10 Prescription Packs)

Attention Pharmacist: Dispense with enclosed Medication Guide.

Rx only

CAUSES BIRTH DEFECTS



isotretinoin capsule

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:10631-115
Route of Administration	ORAL	DEA Schedule	

	Active Ingredient/Active Moiety		
l	Ingredient Name	Basis of Strength	Strength
l	ISOTRETINO IN (UNII: EH28 UP18 IF) (ISOTRETINO IN - UNII: EH28 UP18 IF)	ISOTRETINOIN	10 mg

Inactive Ingredients	
Ingredient Name	Strength
SOYBEAN OIL (UNII: 241ATL177A)	
SORBITAN MONOOLEATE (UNII: 06 XEA2VD56)	
PROPYL GALLATE (UNII: 8 D4SNN7V92)	
TITANIUM DIO XIDE (UNII: 15FIX9 V2JP)	
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	
POTASSIUM HYDROXIDE (UNII: WZH3C48M4T)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
SHELLAC (UNII: 46 N10 7B710)	
PEG-32 HYDRO GENATED PALM GLYCERIDES (UNII: G6 EP177239)	
GELATIN (UNII: 2G86QN327L)	

Product Characteristics				
Color	YELLOW (yellow)	Score	no score	
Shape	CAPSULE	Size	18 mm	
Flavor		Imprint Code	G;240	
Contains				

Packaging			
# Item Code	Package Description	Marketing Start Date	Marketing End Date
1 NDC:10631-115-31	3 in 1 BOX		
1 NDC:10631-115-69	10 in 1 BLISTER PACK		

Marketing Information				
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date	
NDA	NDA021951	06/08/2012		

ABSORICA

isotretino in capsule

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:10631-116
Route of Administration	ORAL	DEA Schedule	

l	Active Ingredient/Active Moiety				
l	Ingredient Name	Basis of Strength	Strength		
l	ISOTRETINO IN (UNII: EH28 UP18 IF) (ISOTRETINO IN - UNII: EH28 UP18 IF)	ISOTRETINOIN	20 mg		

Inactive Ingredients	
Ingredient Name	Strength
SOYBEAN OIL (UNII: 241ATL177A)	
SORBITAN MONOOLEATE (UNII: 06XEA2VD56)	
PROPYL GALLATE (UNII: 8D4SNN7V92)	
TITANIUM DIO XIDE (UNII: 15FIX9 V2JP)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	
POTASSIUM HYDROXIDE (UNII: WZH3C48M4T)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
SHELLAC (UNII: 46N107B71O)	
PEG-32 HYDRO GENATED PALM GLYCERIDES (UNII: G6EP177239)	
GELATIN (UNII: 2G86QN327L)	

Product Characteristics				
Color	RED (red)	Score	no score	
Shape	CAPSULE	Size	22mm	
Flavor		Imprint Code	G;241	
Contains				

Packaging			
# Item Code	Package Description	Marketing Start Date	Marketing End Date
1 NDC:10631-116-31	3 in 1 BOX		
1 NDC:10631-116-69	10 in 1 BLISTER PACK		

Marketing Information				
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date	
NDA	NDA021951	06/08/2012		

ABSORICA

isotretinoin capsule

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:10631-117
Route of Administration	ORAL	DEA Schedule	

Active Ingredient/Active Moiety		
Ingredient Name	Basis of Strength	Strength
ISOTRETINO IN (UNII: EH28 UP18 IF) (ISOTRETINO IN - UNII: EH28 UP18 IF)	ISOTRETINOIN	30 mg

Inactive Ingredients	
Ingredient Name	Strength
SO YBEAN OIL (UNII: 241ATL177A)	
SORBITAN MONOOLEATE (UNII: 06XEA2VD56)	
PROPYL GALLATE (UNII: 8D4SNN7V92)	
TITANIUM DIO XIDE (UNII: 15FIX9 V2JP)	
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	
FERROSOFERRIC OXIDE (UNII: XM0 M8 7F357)	
POTASSIUM HYDRO XIDE (UNII: WZH3C48 M4T)	
PO VIDO NES (UNII: FZ989GH94E)	
PROPYLENE GLYCOL (UNII: 6 DC9 Q16 7 V3)	
SHELLAC (UNII: 46 N10 7B710)	
SO DIUM HYDRO XIDE (UNII: 55X04QC32I)	
PEG-32 HYDRO GENATED PALM GLYCERIDES (UNII: G6EP177239)	
GELATIN (UNII: 2G86QN327L)	

Product Characteristics				
Color	BROWN (brown)	Score	no score	
Shape	CAPSULE	Size	23mm	
Flavor		Imprint Code	G;242	
Contains				

F	Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date	
1	NDC:10631-117-31	3 in 1 BOX			
1	NDC:10631-117-69	10 in 1 BLISTER PACK			

Marketing Information			
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA021951	06/08/2012	

isotretinoin capsule

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:10631-118
Route of Administration	ORAL	DEA Sche dule	

Active Ingredient/Active Moiety			
Ingredient Name	Basis of Strength	Strength	
ISOTRETINO IN (UNII: EH28 UP18 IF) (ISOTRETINO IN - UNII: EH28 UP18 IF)	ISOTRETINOIN	40 mg	

Inactive Ingredients	
Ingredient Name	Strength
SO YBEAN OIL (UNII: 241ATL177A)	
SORBITAN MONOOLEATE (UNII: 06XEA2VD56)	
PROPYL GALLATE (UNII: 8D4SNN7V92)	
TITANIUM DIO XIDE (UNII: 15FIX9 V2JP)	
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	
FERROSOFERRIC OXIDE (UNII: XM0 M8 7F357)	
POTASSIUM HYDRO XIDE (UNII: WZH3C48 M4T)	
PO VIDO NES (UNII: FZ989GH94E)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
SHELLAC (UNII: 46 N107B710)	
SODIUM HYDROXIDE (UNII: 55X04QC32I)	
PEG-32 HYDRO GENATED PALM GLYCERIDES (UNII: G6EP177239)	
GELATIN (UNII: 2G86QN327L)	

Product Characteristics				
Color	BROWN (brown, red), RED	Score	no score	
Shape	CAPSULE	Size	25mm	
Flavor		Imprint Code	G;325	
Contains				

Packaging			
# Item Code	Package Description	Marketing Start Date	Marketing End Date
1 NDC:10631-118-31	3 in 1 BOX		
1 NDC:10631-118-69	10 in 1 BLISTER PACK		

Marketing Information			
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA021951	06/08/2012	

isotretino in capsule

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:10631-133
Route of Administration	ORAL	DEA Schedule	

ı	Active Ingredient/Active Moiety		
ı	Ingredient Name	Basis of Strength	Strength
ı	ISOTRETINO IN (UNII: EH28 UP18 IF) (ISOTRETINO IN - UNII: EH28 UP18 IF)	ISOTRETINOIN	25 mg

Inactive Ingredients		
Ingredient Name	Strength	
SO YBEAN OIL (UNII: 241ATL177A)		
SORBITAN MONOOLEATE (UNII: 06 XEA2VD56)		
PROPYL GALLATE (UNII: 8 D4SNN7V92)		
TITANIUM DIO XIDE (UNII: 15FIX9 V2JP)		
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)		
SHELLAC (UNII: 46 N10 7B 710)		
SODIUM HYDROXIDE (UNII: 55X04QC32I)		
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)		
FD&C YELLOW NO. 5 (UNII: I753WB2F1M)		
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)		
PO VIDO NES (UNII: FZ989 GH9 4E)		
PEG-32 HYDRO GENATED PALM GLYCERIDES (UNII: G6EP177239)		
GELATIN (UNII: 2G86QN327L)		

Product Characteristics			
Color	GREEN (green)	Score	no score
Shape	CAPSULE	Size	22mm
Flavor		Imprint Code	G;342
Contains			

Packaging				
# Item Code	Package Description	Marketing Start Date	Marketing End Date	
1 NDC:10631-133-31	3 in 1 BOX			
1 NDC:10631-133-69	10 in 1 BLISTER PACK			

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA021951	06/08/2012	

isotretinoin capsule

Product Information

Inactive Ingredients

GELATIN (UNII: 2G86QN327L)

 Product Type
 HUMAN PRESCRIPTION DRUG
 Item Code (Source)
 NDC:10631-134

 Route of Administration
 ORAL
 DEA Schedule

Active Ingredient/Active Moiety

PEG-32 HYDROGENATED PALM GLYCERIDES (UNII: G6EP177239)

Ingredient Name
Basis of Strength
ISOTRETINO IN (UNII: EH28 UP18 IF) (ISOTRETINO IN - UNII: EH28 UP18 IF)
ISOTRETINO IN (UNII: EH28 UP18 IF) ISOTRETINO IN 35 mg

Ingredient Name SOYBEAN OIL (UNII: 241ATL177A) SORBITAN MONO OLEATE (UNII: 06 XEA2VD56) PROPYL GALLATE (UNII: 8D4\$NN7V92) TITANIUM DIO XIDE (UNII: 15FIX9 V2JP) PROPYLENE GLYCOL (UNII: 6DC9Q167V3) SHELLAC (UNII: 46N107B71O) SODIUM HYDRO XIDE (UNII: 55X04QC32I) FD&C BLUE NO. 2 (UNII: L06K8R7DQK) POVIDONES (UNII: FZ989GH94E) FERROSOFERRIC OXIDE (UNII: XM0 M87F357) FERRIC OXIDE RED (UNII: 1K09F3G675) FERRIC OXIDE YELLOW (UNII: EX438O2MRT)

Product Characteristics			
Color	BLUE (blue)	Score	no score
Shape	CAPSULE	Size	23mm
Flavor		Imprint Code	G;343
Contains			

Pa	ckaging			
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1 1	NDC:10631-134-31	3 in 1 BOX		
1 1	NDC:10631-134-69	10 in 1 BLISTER PACK		

Marketing Information			
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA021951	06/08/2012	

Labeler - Ranbaxy Laboratories Inc. (169932519)

Registrant - Galephar Pharmaceutical Research Inc. (003551624)

Establishment			
Name	Address	ID/FEI	Business Operations
Galephar Pharmaceutical Research Inc.		003551624	ANALYSIS(10631-115, 10631-116, 10631-117, 10631-133, 10631-134, 10631-118), MANUFACTURE(10631-115, 10631-116, 10631-117, 10631-118, 10631-133, 10631-134), PACK(10631-115, 10631-116, 10631-117, 10631-118, 10631-133, 10631-134)

Establishment			
Name	Address	ID/FEI	Business Operations
BASF PharmaChemikalien GmbH & Co. KG		328633636	API MANUFACTURE(10631-115, 10631-116, 10631-117, 10631-118, 10631-133, 10631-134)

Revised: 8/2014 Ranbaxy Laboratories Inc.